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GENERAL PRACTICE CLINICS

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CLINICAL MEDICINE

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TOLERANCE OF MAN FOR ISONICOTINYLHYDRAZINES — *Roger A. Lewis*

MEDICAL HUMANITIES

THE HISTORY OF ENDOCRINOLOGY AS SEEN THROUGH THE EVOLUTION OF OUR KNOWLEDGE OF THE ADRENAL GLAND — *Félix Martí Ibáñez*

PAN AMERICAN MEDICAL WOMAN'S SECTION

SYMPTOMATOLOGY OF STUTTERING — *Elly Sittig*

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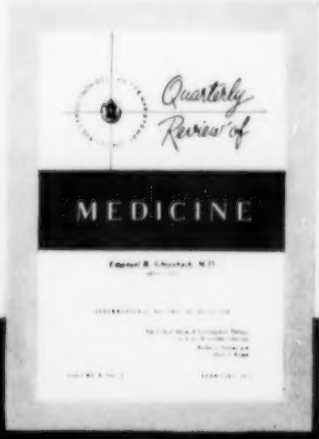

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Selman A. Waksman Receives Nobel Prize

"I can hardly find the proper words to express my feelings in this matter. This is the culminating point of my life's work, begun in 1915 with the study of a humble group of soil micro-organisms, the actinomycetes, which have yielded in recent years some of the greatest benefits to mankind.

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"I feel particularly proud for the field of science which I represent, microbiology, and for the institution where I have done my major work. . . . I feel proud in justifying the ancient saying 'And from the earth shall come thy salvation'; and that the micro-organisms that have yielded these important chemical substances which are used in the healing of human diseases should come from the soil."

These words were spoken by Selman A. Waksman as he received the news that he had been awarded the 1952 Nobel Prize in medicine.

The award was given to Dr. Waksman in appreciation of his discovery of the antibiotic, streptomycin, in 1943. Although streptomycin is used to combat bubonic plague, tularemia, whooping cough, and urinary infections, Dr. Waksman received the prize exclusively for the drug's usefulness against tuberculosis.

The Editorial Board of the INTERNATIONAL RECORD OF MEDICINE is particularly proud that they have had the opportunity to publish a highly interesting commentary on the life and work of the man known as the "Father of Chemotherapy," suitably written by one of the most prominent microbiologists of our times. This paper, "The Living Thought of Paul Ehrlich" by Selman Waksman, appeared in the May 1952 issue of this journal. We are also proud to say that Selman Waksman is an active member of the National Editorial Board of ANTIBIOTICS AND CHEMOTHERAPY, another publication of the Washington Institute of Medicine.

Tolerance of Man for Isonicotinylhydrazines*

Roger A. Lewis

DEPARTMENT OF CLINICAL RESEARCH

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The advent of isonicotinylhydrazines as antituberculosis drugs has been reviewed in an editorial of the *Journal of the American Medical Association*,[1] which summarizes the papers published in the January issue of the *Quarterly Bulletin of the Sea View Hospital* and the April issues of the *American Review of Tuberculosis* and *Diseases of the Chest*. Although aromatic derivatives of hydrazines have been used in medicine, this is the first time that nonaliphatic derivatives of hydrazides have been employed as drugs and the first time that either hydrazines or hydrazides have been used as chemotherapeutic agents.

The rapid expansion of clinical studies and the continued observation of cases already reported has given rise to some evidence of "late toxicity" which was suggested by the animal studies and anticipated in the clinical reports. Furthermore, there has been ample confirmation of the original description of disturbances of nervous system function and indications of circumstances under which these effects may be more frequent or severe.

There is also available additional information on the blood levels and urinary excretion of both isonicotinylhydrazine and 1-isonicotinyl-2-isopropyl hydrazine which contains no free NH_2 group. The degradation product—isonicotinic acid—has been identified and measured both in the blood and urine of experimental animals and human subjects treated with either of these two drugs.

In the light of these confirmatory and new observations on the physiology and pharmacology of the isonicotinylhydrazines, it seems appropriate to evaluate and emphasize the maximum safe limits of dosage.

NERVOUS SYSTEM TOXICITY

In a series of 73 patients studied for 9 to 15 weeks at a daily dose level of 2 to 4 mg. per Kg. of body weight of isonicotinyl-isopropyl-hydrazine (Marsilid),† certain disturbances of the nervous system were noted.[2] Of these the most prominent were vertigo, twitching of the lower extremities, headache, visual difficulties, and drowsiness or insomnia. Also noted and thought to be related to the autonomic nervous system were postural hypotension, constipation, delay in initiation of micturition, and dryness of the mouth. Similar symptoms were noted, although less frequently, in a smaller number of cases treated for a shorter period with the parent compound, isonicotinylhydrazine (Rimifon).†

*This article originally appeared in *Antibiotics & Chemotherapy*, 6:285-89, 1952.

†Trademark, Hoffmann-La Roche Inc., Nutley, N. J.

The symptoms experienced by these patients are reminiscent in some respects of those described by patients treated with the antihypertensive agent 1-hydrazinophthalazine, an aromatic hydrazine derivative.[2] The administration of 100 to 600 mg. daily of this drug may produce headache, dizziness, and postural hypotension. However, in the case of the isonicotinylhydrazines, the blood pressure is not lowered except at the time when vertigo is experienced and then not in all cases.

Similar symptoms also have been reported in patients treated with hexamethonium compounds which produce ganglionic blockade and inhibition of the parasympathetic nervous system. Such symptoms may be relieved by the administration of prostigmine.[2a]

One group of observers did not encounter any evidence of drug toxicity in a group of 6 patients treated for six weeks with 3 mg. per Kg. of body weight of isonicotinylhydrazine (Nydrazide).[3] However, reports from other groups have confirmed the occurrence of signs and symptoms of dysfunction of the nervous system in patients treated with isonicotinylhydrazine (Rimifon) at dose levels of 1 to 8 mg. per Kg. of body weight.[4-6] Among the disturbances noted was the occurrence of evanescent convulsions in a patient receiving 4 mg. per Kg. of body weight.[4]

Occasional patients receiving isonicotinylhydrazine (Rimifon), or its isopropyl derivative (Marsilid), for a period of months have manifested an increased central nervous system irritability including clinic seizures when hypnotic or anesthetic drugs (Demerol) were administered.[4,13]

The incidence and severity of these reactions is greater in patients with renal disease,[5] in patients who are anemic, in older individuals, and at higher dose levels.[8] The same symptoms can occur, albeit less commonly in young adults with normal renal function and normal blood hemoglobin level at a dose level of 4 mg. per Kg. of body weight. These symptoms are especially important in ambulatory patients who may have to be treated with relatively small doses.

HEPATIC TOXICITY

Hepatic damage has been observed in rats and dogs following the administration of isonicotinylhydrazine.[9] The isopropyl compound appears to be less toxic in this respect, and in the monkey does not produce liver damage at high dose levels.[10] In fact, the liver changes noted in dogs and rats when this derivative is administered may be in part the result of increased pigment deposition due to destruction of red blood cells.

In a few patients treated with isonicotinylhydrazine (Rimifon) the cephalin flocculation test has become abnormally positive.[7,8] Apparently at comparable dose levels this laboratory evidence of hepatic damage is more frequent and more pronounced in patients treated with the parent compound than in cases treated with isonicotinyl-isopropylhydrazine (Marsilid). One patient treated with 15 mg. per Kg. of body weight with the latter drug showed slight evidence of hepatic injury when the liver was examined histologically. It may be anticipated that as more patients are brought under treatment, and especially if the dose of drug is increased, there will occur cases of hepatitis and/or icterus.

On the other hand, several cases with hepatic damage due to cirrhosis or amyloidosis have been treated with the isopropyl derivative without ill effect.[8]

ANEMIA

Increased red blood cell destruction is produced by the administration of phenylhydrazine or acetylphenylhydrazine. Both of these compounds have been used in the treatment of polycythemia vera[11,12] and have been administered at dose levels of 25 to 200 mg. daily for as long as seven years.

The isonicotinylhydrazines have similar but less pronounced hemolytic action. Both in patients[8] and experimental animals,[9] it has been observed that the isopropyl derivative is more active in this respect. The slight lowering of the hemoglobin level observed in patients treated with the isonicotinylhydrazines at three to six weeks is self-limited and tends to disappear while treatment is continued. However, if the dose of isonicotinyl-isopropylhydrazine (Marsilid) is raised to 8 mg. per Kg. of body weight, the fall in hemoglobin level may be significant.

Fortunately, the only marked changes in leukocytes that have been observed consist in an increase in the total number and a transient eosinophilia. Patients with sickle cell anemia have undergone treatment without difficulty.[8] The incidence of nervous system disturbances may be higher in anemic patients.

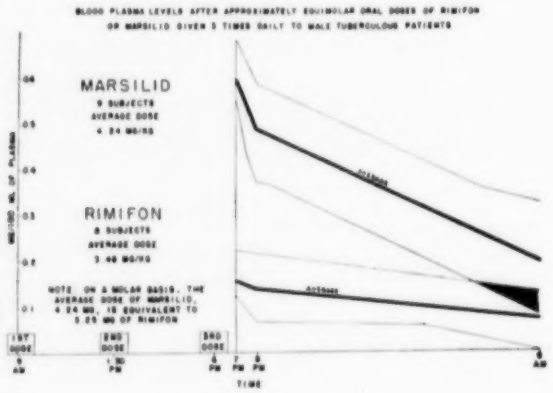

FIG. 1. Blood plasma levels after approximately equimolar oral doses of Rimifon or Marsilid given three times daily to male tuberculous patients

RENAL TOXICITY

Although albuminuria and the presence of formed elements in the urinary sediment have been noted in tuberculous patients while under treatment with the isonicotinylhydrazines, there is no evidence that this is a direct effect of the drugs. Such occurrences are sporadic and unrelated to dosage.

Few blood level observations are available in patients with renal damage or solitary kidney treated with isonicotinylhydrazines, but the incidence of nervous system toxic reactions is greater in such cases,[6] especially when high doses are used.

There are a few instances on record of patients with an elevated nonprotein nitrogen (NPN) level of the blood that have been treated with the isonicotinylhydrazines. Apparently such treatment was well tolerated since the NPN gradually diminished during the therapy.[8,9] Nevertheless, it would seem prudent to use relatively small doses of the isonicotinylhydrazines in patients with renal dysfunction, except where blood levels can be followed.

BLOOD LEVELS AND URINARY EXCRETION

The rapid adsorption, distribution, and excretion of isonicotinylhydrazines has been reported.[4] No distinction was made between the active drug and its degradation product, isonicotinic acid.[4] While the latter is present only in small amounts in the blood of patients on low doses, it constitutes approximately 50 per cent of the total of excreted products.[13] Apparently isonicotinyl-isopropyl-hydrazine (Marsilid) is excreted more slowly than isonicotinylhydrazine (Rimifon), so that with the same dose considerably higher blood levels are achieved.

In most studies, these drugs were given three times a day in equally divided doses at meal time. Under such circumstances the maximum blood level would occur approximately one hour after the last daily dose and the minimum blood level on the next day just prior to the first dose. In figure 1 the blood plasma levels are given for both drugs, the samples being taken at the times indicated above. It can be seen readily that the minimum level achieved with isonicotinyl-isopropyl-hydrazine (Marsilid) is higher than the maximum level achieved with isonicotinylhydrazine (Rimifon).

At the present time it is not known in what manner—if any—the blood level of these drugs is correlated with toxic manifestations or therapeutic effects. In fact, the hyper-reflexia, and lowered threshold for clonic seizures may persist several days after treatment is discontinued and at a time when the amount of drug in the blood is negligible.

THERAPEUTIC DOSAGE

Therapeutic results achieved by different investigators working with various dose regimes suggest that the minimal effective dose of isonicotinylhydrazine (Rimifon) varies between 1 and 2 mg. per Kg. of body weight.[5-8] The minimal effective dose of isonicotinyl-isopropyl hydrazine (Marsilid) has been estimated to lie between 0.5 and 1.5 mg. per Kg. of body weight.[8] These estimates are compatible with the impression that contrary to *in vitro* and animal experiments, the isopropyl derivative (Marsilid) is the more active drug in human tuberculosis.[8-14] These estimates are presented to justify the currently advocated dose range of 2 to 4 mg. per Kg. of body weight for both drugs. It is likely that further improvements in therapy will result from the use of new derivatives rather than from the administration of doses larger than those currently recommended.

In the series of cases being treated under the auspices of the Army-Navy-Veterans Administration Committee on the Chemotherapy of Tuberculosis, a dose level of 150 to 300 mg. per patient per day was selected. It would seem prudent to adhere to

conservative dosage regimes until results of this large and important study are reported.[15]

Although pregnancy, type of tuberculosis, sex, and race seem to have little effect on the toxicity of the isonicotinylhydrazines, older subjects, patients with anemia or reduced renal function, and ambulatory patients should be treated with conservative doses. Special care is advised in the treatment of patients with a history of mental disturbance. The possibility of an increased tuberculin reaction makes it desirable to use low doses in the treatment of patients with a tendency toward allergic reactions. Special caution should be observed in the concurrent administration of adrenergic, hypnotic and anesthetic drugs. Improved circulation in tuberculous patients may lead to hemoptysis[8] or hemorrhage from wounds. With the rapid gain in weight exertional dyspnoea may be aggravated and cardiac disturbances precipitated.[8]

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Figure 1 was supplied through the courtesy of E. H. Robitzek, I. J. Selikoff, E. Mamlok and J. A. Rogers, Sea View Hospital and S. H. Rubin, L. Drekter, J. Scheiner and E. De Ritter, Jr., Hoffmann-La Roche Inc., Nutley, New Jersey.

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MEDICAL HUMANITIES

The History of Endocrinology as seen through the Evolution of our knowledge of the Adrenal Gland

BIOGRAPHY OF A MEDICAL IDEA

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I. THE THEORY OF THE "TIME-AXIS" IN HISTORY

Karl Jaspers, psychiatrist and philosopher, has applied to research in History the theory of the "time-axis", designating that supremely important moment in the evolution of nations when modern humanism and culture began to flower.

As Jaspers has shown, it is not possible to understand the make-up of a cultural problem unless it is placed within the over-all framework of universal history, since only by viewing History as a whole can we understand our individual destinies. We must therefore make of History something contemporaneous, and change it from a matter of mere aesthetic curiosity into the oft-painful task of understanding ourselves.

It is not possible to evaluate the progress and goals of any branch of Medicine except in the light of its origin and development, factors which also allow us to study its future tendencies. Only by conceiving the History of Medicine as a unit and perceiving its meaning can we give it an architectonic structure.

The beginning of the most powerful cultural forces of man took place, according to Jaspers, in the year 500 B.C., a time-axis when man as we know him today appeared. In three world regions entirely independent from each other—China, Greece and India—a gigantic spiritual movement started to develop in which man became conscious of himself, aspired to self-liberation, and asked himself great spiritual questions which became the bases of the philosophical and religious categories that

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guide our thought today. What happened then was so fundamental that everything that came before it was simply preparation and everything that came after a mere sequel.

The strange chronological parallelism of the time-axis in those three cultures, where the historical-cultural evolution of modern peoples started, must have originated in the sudden appearance of tribes of horsemen with war-chariots from Central Asia, who introduced the horse into the aforementioned areas. The invaders knew how huge the world was; they had "conquered and ruled ancient cultures; were conscious of the problems of living and were responsible for a crucial turn in History"; they reached the Mediterranean and Europe at the end of the third millennium B.C.; by 1200 B.C. they reached India, and invaded China and Iran at the end of the second millennium before Christ. Those nations of horsemen finally came face to face with the ancient, narrow, matriarchal, cattle-breeding, sedentary cultures.

In Medicine, time-axes also exist: they are basic periods during which the seeds of medical progress are planted and tremendous leaps in the history of Science are made. Among those time-axes in Medicine we distinguish periods such as human Hippocratic medicine which is naturalistic and observational; the liturgical, psychotherapeutic and hypnotic cult of Aesculapius; the school of Alexandria; the era of Galen; Vesalius; Paracelsus; Harvey and the experimental method; and the time-axis of Thomas Addison marking the origin of modern Endocrinology. The years running from 1849—when Addison made his first report on the adrenal gland—to our day constitute a time-axis, a fertile century for the development of Endocrinology, which, although the youngest of medical sciences, offers the greatest promise, and perhaps contains the secret of the Medicine of the future.

In those portentous two periods of half a century each, the first of which brings us to the beginning of our century and the second of which brings us up to date, the bases not only of Endocrinology but also of a new view of Medicine were laid.

II. PRELUDE TO THE HISTORY OF ENDOCRINOLOGY

The history of Endocrinology[1] is still to be written; our sole aim here is to present its basic stages as seen through the evolution of our knowledge of the adrenal gland. Just as we would have to review the entire history of Psychiatry in order to trace the history of ideas concerning schizophrenia, just as we would have to know the entire evolution of Neurology in order to write the history of epilepsy, we have to unwind the philosophico-historical thread which pulls through the evolution of all endocrinological ideas in order to study the development of ideas concerning the adrenal gland.

As far as our study is concerned, the last half of the XIX century is highlighted by only a few events, but these are of monumental importance because they are the foundations on which modern Endocrinology was erected. Their dates are: 1849, when Addison published the first written report in the history of Medicine correlating a clinical syndrome with a lesion of the endocrine glands; 1891, when Murray in England treated a myxedematous patient for the first time with a thyroid extract; and 1899, when Brown-Séquard propounded his notion of the existence of a mechanism

of endocrine integration in the organism different from that of nervous integration. Perhaps the first date—1849—should be considered as marking the birth of modern Endocrinology, since it was the brilliant work of Addison which would result years later in the development of a new view and new method, if not in the field of research into endocrine diseases at least in tackling the problems of Medicine and Biology.

The history of our ideas concerning the adrenal gland not only embraces the history of all of Endocrinology, but may also be used to study the evolution of modern medical thought, especially the introduction into Medicine of the new philosophico-biological concepts related to the adrenal cortex, concepts which may hold the key to the Medicine of the next half century. We shall study these ideas rather than the men who formulated them, and sacrifice the anecdotal to the substantive. In this way we shall be situating the ideas in time and projecting the concept of the role of the adrenal gland over physical space which embraces both the scientists concerned and the historical course of our grasp of that role.

It has been said that Medicine is entering an "Adrenal Era". Although this may be an exaggeration, we must recognize the fact that the biography of the "adrenal idea" contains the germs of many modern methods of medical experimentation.

This task of trying to revive the endocrinological past is one of the most fascinating a scientist can undertake. It can help not only to resuscitate the past, but to anticipate what is yet to come. For in reviewing the ground covered by endocrinological thought, he may find that at certain points he can jump from the diving-board of thought to the horizons of the future.

History is a tremendous attempt at resurrection. And to resurrect is not to expose the bones of the past to the light but to restore the vitality of that past and divine the forces which impelled it when it was alive. To understand the endocrinological bridge which is under construction means to project into the future its dynamic curve and apprehend onto what portion of tomorrow's shores the rest of the arch will fall.

The history of Endocrinology is of enormous importance at the present moment, when the endocrine system and its nervous correlations have opened up fresh paths for research into the problems of the human being in health and illness. It offers a gigantic lesson in methodology: it teaches us not to disdain theoretic and interpretive thought, a notion revindicated by Selye when he affirmed that such thought is of supreme importance in endocrinological research because endocrine correlations, the basis of modern Endocrinology, can only be elucidated after a plan has been sketched to coordinate related facts theoretically on the basis of available knowledge.

III. THE GREAT NEGLECT: BIOGRAPHY OF AN IDEA

The adrenal gland was for a long time neglected in the history of medicine. A curious combination of factors contributed to the fact that adrenal physiology and pathology were incorporated quite tardily into the sum of medical knowledge. Some of these factors are: the hidden anatomical location of the gland; the effects which the delay in performing dissections (done clandestinely for many centuries) had on said gland, converting its inner tissues into an amorphous mass as a result of the autolytic process; proximity of the gland to the kidneys because of which it

resembled an excretory gland; the lack of correlation between this gland and the clinical syndrome motivated by it; and the extraordinary difficulties in clinically isolating its hormones. But when adrenal physiology was finally understood, it revolutionized a great number of medical, diagnostic, therapeutic and biological concepts, and initiated a philosophico-scientific revolution in modern Biology.

"Writing History," Ortega y Gasset has said, "is an enthusiastic attempt at resurrection." In this essay, we shall make an attempt at writing an introduction to the biography of the "adrenal concept" in Medicine, at presenting the evolution of the idea of the adrenal gland along with the thoughts of some of the men who worked to extricate its clinical, physiological, chemical and biological secrets. As we do that, we shall also be tracing the panorama of Endocrinology, for the history of the study of the adrenal gland—its failures, its victories, and the brilliant work being done now as a result of the triumph of experimental thought over authoritarian tradition in Medicine—summarizes the eternal conflict between clinical experimentation and intransigent dogmatism, which in turn summarizes the *entire* history of Science.

IV. AGE-OLD ORGANOTHERAPY

It is highly significant that when in 1849—the date we have chosen as signalizing the beginning of modern Endocrinology—the scrutinizing eyes of Thomas Addison discovered lesions in the adrenal glands of a corpse and related them to the clinical syndrome he had observed when the patient was alive, very little was known about the ductless glands.

The majority of these glands had already been described, but up to then nobody had pointed out the importance of their functions in the organism. The anatomists of all times had been accustomed to looking for glands with an excretor duct, the morphology of which provided them with the key to the functions of those glands. They had no conception of glands without an excretor duct. The unanimous tendency therefore was to consider the latter simply as ontogenic survivals, relics of atrophied organs, or mere organic formations with insignificant excretory functions.

Man discovered the therapeutic use of these glands before understanding their function. Empiric organotherapy historically precedes scientific endocrinology by more than a millennium.[3] It is scarcely half a century that the function of all the endocrine glands has been understood, but we have been aware from time immemorial of the correlation which exists between the form of our body, the mechanism of our emotions, and the action of certain endocrine glands. Primitive warriors used to devour the heart, liver, and other innards of their enemies killed in combat so that they might assimilate the warlike virtues which they believed to be immanent in said innards. Those primitive peoples who situated the qualities of courage and ferocity in certain inner organs, practiced rudimentary opotherapy because in addition to their nutritive value those organs had the psychological value of furnishing the victorious warrior full confidence in the fact that he had increased his own courage by making the bloody entrails of his adversary part of his own flesh. In the *Ebers Papyrus*, the medical bible of ancient Egypt, glandular extracts are among the 700 medicaments cited.

The most ancient mystical insight into the existence of the adrenal glands and the physiological role they play may be found in the ancient metaphysics of the *chackyas*.[3] The first trace of the theory is to be found in the book *Yogasikha* of the Hamsa Upanishad, whence, after several centuries, it passed over into the Tantras or sacred books of the *Saktas*. These books expound the idea of the spiritual power inherent in the body in the form of a *Kundalini* which lies "curled like a serpent" at the level of a "vital center or Chackra" called the *muladhara*, situated "at the bottom of the spinal column." From this center, when the power is stimulated by ascetic discipline, it ascends "through a series of seven centers" or *chackras* (a word meaning "wheel," "that which turns" in Sanscrit). This theory was revived in the Yoga of Patanjali and Vyasa, and in later Indian philosophies. The strange part of all this is that the location and functions of these centers of energy or *chackras*, not only in philosophical descriptions but also in ancient Hindu mystical iconography,[4] coincides exactly with the ductless glands. We can conclude therefore that the ancient mystical books of India have contained for more than three thousand years descriptions of the location and functions of the adrenal gland, identified by them as the so-called "sacred center" or *svadishthana*.

The most ancient reference extant to an endocrine disease is to be found in the Artharva Veda, a collection of Hindu religious rites written in India before 1500 B.C., which contains an enchantment recited by the Buddhist bonzos to cure goiter patients. In the Ayurva-Veda of Susruta (1400 B.C.) a case of goiter is described.

Aristotle (384–322 B.C.) recommended organotherapy. The Elder Pliny (23–79 A.D.) dedicated books XXVIII to XXXII of his *Natural History* to *materia medica*, and studied the medicines derived from animal and human organs. Hippocrates was the first to make a nosographic study of hypo-orchidism, a disease of the Scythians, and of climacteric hypoovarism, connecting certain symptomatic complexes with endocrine alterations. The Alexandrine doctors in the third century B.C. described the gonads and the liver. Areteus of Cappadocia (150 B.C.) described diabetes, although he attributed it to a renal poison of the bladder injected by the bite of a poisonous snake. The Greeks and Romans knew of diabetes mellitus, and Celsus, the elegant Roman doctor (30–50 B.C.), knew of polyuria, polydypsia and emaciation of the diabetic patient. In his autopsies on monkeys, Galen found the thymus—he compared it to a bunch of thyme leaves, which accounts for the name he gave it—the thyroid, the pituitary and the epiphysis glands. For him the pituitary acted as a sieve for humidity and discharge of fluids from the brain to the nasopharynx. In his work *De Voce*, he vaguely described the thyroid as part of the vocal apparatus. Juvenal, Pliny and Paracelsus also described it. In 1180, Roger of Palermo treated goiter with marine sponges and sea-weed rich in iodine, a method already used in China (1600 B.C.) thousands of years before iodine was discovered.

Paracelsus (1493–1541), the father of pharmaceutical chemistry, justified opotherapy with his *similia similibus curantur*; he felt that the best method of curing a diseased organ was to administer another similar organ, thus initiating therapy by substitution.

In 1755 Theophile de Bordeu, of Montpellier, in his *Analyse médicinale du sang* expressed the opinion that all organs produce specific substances which pass into the blood and are useful to the organism; he indicated that the deficitary symptoms of castrates might come from a lack of the humoral substances produced by the sex glands, and expressed the idea that the anomalies of humoral secretions play an important role in pathology (*"C'est au médecin à suivre et à classer les divers reflux qui surviennent par la faute de chaque organe en particulier"*).[5] But the predominant opinion that integration of the activities of distant organs is performed in our organism by the nervous system, solidly established by Descartes in the 17th century and then confirmed by the Viennese physiologist Prochaska (1784), were obstacles in the way of the recognition of endocrine activity as a process of organic physiological correlation.

Berthold de Gottingen (1849) indicated that the testicles possess an internal secretion, and proved that by castration it was possible to destroy secondary sex characteristics in cocks, and develop them through testicular implantations.

V. THE ADRENAL GLAND BEFORE ADDISON: THE MORPHOLOGICAL PERIOD

Before Addison's time, the adrenal gland (as well as the other endocrine glands) had been described by the ancient anatomists who were, nevertheless, incapable of attributing any important function to it. Ancient anatomy was a static branch of medicine, and working on the corpse accentuated that staticism, for it was thought that only those organs whose anatomical configuration seemed to help in the understanding of the existence of some vital physiological function inherent in these organs were important for life. When it was a question of glands for which no duct could be found, these organs could only be considered—as happened with the endocrines—as unimportant anatomical vestiges. In the case of the adrenal glands, their position and exiguous size contributed to making them unimportant in the eyes of anatomists. When we consider this matter in the light of the new theories concerning the all-important role played by the adrenal cortex in all the phases of human life, we come to the conclusion that it is time to write a *true* adrenal interpretation not as part of the history of Medicine but as part of History in general, and revindicate not so much the role of this vital gland in the history of the diseases of mankind, as its influence on the decisions, maladies, and vicissitudes of man, in short, on the destinies of nations.

Two centuries after the description of the adrenals had been made in 1563 by Bartholomeus Eustaquius (1520–1574),[6] these glands—which he called *"glandulae renibus incumbunt"*—had been catalogued as mere anatomical curios.

In 1607, Jean Riolanus (1577–1657), professor of Anatomy on the Faculty of Medicine in Paris and a follower of Galen and Descartes, referred to them as *"capsulae suprarrenale."* But the secret of the functional role played by these glands lay dormant in the copper plates engraved by Eustaquius for his *Tabulae Anatomica* and which he had completed years before the publication of Vesalius' *De Humanis Fabrica Corporae*. These *Tabulae Anatomica*, because of economic and other difficulties, did not appear during the lifetime of the author. For 138 years, until they were re-

discovered by Lancisi in the Vatican Library, these plates were unknown. Unfortunately, Pope Clement XI did not permit his physician Lancisi to publish them until 1673. By one of those ironic paradoxes of History, the mysterious disappearance of the copper plates, whose illustrations, although less artistic than those of Vesalius, were more exact, determined their publication after that of the *Fabrica*; if that had not happened, Eustaquius would have been considered, along with Vesalius, the co-founder of modern anatomy.

In 1627 Spigelius had mentioned these glands as "*capsulae renale*." In 1687 Malpigio stated that the name of "*capsulae suprarrenale*" should be rejected because it expressed only the aspect of central liquefaction produced by autolysis of the corpse.[7]

Significant proof of the profound relationship existing between historical events and the progress of Medicine is contained in the ancient secular terror at touching dead bodies, not to mention performing autopsies. That terror, accentuated by the religious persecution of those who dared to defy prohibition against dissection of corpses, had a retarding effect on the progress of anatomy and medicine, which sciences had to limit themselves to animal dissection for thousands of years. Later, when impatient anatomists began clandestinely to use corpses dug up from cemeteries, autopsies were carried out with great caution, often several days after death, when the adrenal medulla had already become transformed by autolysis into a dark viscous liquid (*atrabilis*) contained within the cortex. That is why it was thought that the adrenals were capsules (*capsulae suprarrenale*) full of liquid. This fact testifies to the close tie existing between the historical *ambiance* of each period and the evolution of Medicine. A religious taboo was able to retard the knowledge of the anatomical structure of the adrenal glands for hundreds of years!

One century after the publication of the *Tabulae Anatomica*, the Academy of Sciences of Bordeaux offered a prize for the best essay on the topic: *What Do the Adrenal Glands Do?* but the prize was not awarded, further proof of how unimportant the problem was considered at the time and how little was known about the gland.

In 1841, Magendie said that no stock should be put in the "*atrabilis negra*" since the adrenal glands *had ceased being* secretory agents. Other scientists, misled by the exiguous dimensions of the gland, believed that they were fetal kidneys whose function had ceased with birth.

Thus ends the first morphological period in the history of the adrenal gland, a period which had yielded only an anatomical description of that organ. When in the year 1849 Addison published his paper, the scientific error of the unimportance of the adrenals was an article of faith among physicians.

As happened with other endocrine glands, an anatomical dogma impeded the development of a scientific truth. Up to that time all important glands had excretory ducts, *ergo* ductless glands did not excrete anything important. Medical research methods proceeding from the organ to its function proved erroneous and harmful, because the descriptions of organs, based always on the dogmatic authority of the ancient anatomists, placed an insuperable obstacle before the new spirit of modern research which based itself on clinical observation and the study of functions.

The next step represents a revolution in methods of clinical study, since for the first time a brilliant mind would offer Medicine not only the description of the first endocrine system, tying it up with its causal gland, but also an extremely original method which, turning its back on anatomical dogma, would come face to face with clinical truth and only then—no earlier—would tie it up with its anatomo-pathological basis. The patient and his symptoms from then on would be the guide to the corpse and its lesions. That was Addison's great contribution.

VI. THOMAS ADDISON AND THE BEGINNINGS OF CLINICAL ENDOCRINOLOGY

Modern Endocrinology was born March 15, 1849, when Thomas Addison made his first report to the South London Medical Society concerning "*a remarkable form of anemia*" invariably connected with lesions of the suprarenal capsules.[8]

Addison's paper is the first report, succinct but so perfect that today we can only add some details of the illness which today bears his name. The importance of this communication—the brevity of which again proves that great scientific discoveries have generally been reported with concision—lies in the fact that, although this was not the first publicized case of diseases like diabetes mellitus, exophthalmic goiter and cortico-adrenal tumors, these disturbances had never been connected with endocrine affections.

At the time he presented his communication, which not only marks the beginning of the scientific study of the adrenal glands but also of Endocrinology in general and which signalizes the transition from morphological to clinical study of the internal secretion glands, Addison was a man of 56 and had been working for 25 years as physician in Guy's Hospital in London. That quarter of a century spent in anonymous silent work in such a splendid institution sharpened his powers of observation and made of him an excellent clinician and a learned pathologist.

Addison lived out his life in an area as circumscribed geographically as it was broad in thought. He was born near Newcastle-on-Tyne in 1793, won for himself a reputation as an outstanding student—he took notes of his teachers' lectures in Latin!—and was graduated from Edinburgh as a physician in 1815. Later he went to London where he practiced in Hatton Garden and was the first surgeon at Lock Hospital; in time he became aid to Dr. Bateman, a famous dermatologist at Snow Hill. But this fashionable professional life held no attractions for him. Loyal to his individual bent, he entered Guy's Hospital as physician in 1824 and remained there until shortly before his death in 1860, eleven years after he made the report which immortalized his name.

At Guy's Hospital Addison worked in close collaboration with Richard Bright, another giant of his time. Fate, it seems, was pleased to unite two men representing two human opposites. Bright was rich, handsome, worldly and popular; Addison was poor, stern, unsociable. Bright spent long periods of time traveling in Cambridge, Berlin, Vienna, Hungary, while Addison had to struggle to make ends meet. Just the same, these men who were united by their intense and sincere interest in clinical problems, were appointed co-professors to occupy the chair of Medicine.

It is possible that close contact with Bright served to increase Addison's timidity, badly hidden beneath a mask of gruffness and haughtiness.

At bottom, Addison was a man of exaggerated shyness and sensibility, perhaps a psychoneurotic, who tried to compensate for the social vacuum in which he lived by devoting himself entirely to his pupils and the hospital. Those who knew him say that he had an outstanding personality, an impression caused perhaps by his imposing physique, abundant beard and penetrating eyes; he was gifted with great powers of clinical observation which, aided by his persistence, sought out the hidden causes of disease.

Let us note what his contemporaries and disciples, Wilks and Bettany (1892), have to say: "For many years he was the leading light of Guy's Hospital, so that every Guy's man during the 30 or 40 years of his teaching was a disciple of Addison. . . . He was dogmatic in his teaching and thus the pupils accepted as pure gospel every word which flowed from his lips. The force of his words was enhanced by his mode of delivery and by the presence of the man himself. . . . His penetrating glance seemed to look through you and his whole demeanor was that of a leader of men enhanced by his somewhat marked attitude. . . . As a teacher, it is difficult to conceive a better. . . . The clinical lectures were most excellent, as he never failed to thoroughly unfold the case which he was discussing. . . . His examination of the patient was of the most complete character; possessing unusually perceptive powers, being shrewd and sagacious beyond the average of men, the patient before him was scanned with a penetrating glance from which few diseases could escape detection. He never reasoned from a half-discovered fact, but would remain at the bedside with a dogged determination to trace out the disease to its very source for a period which constantly wearied the class and his attendant friends. . . ."

Almost the same words are used by the writer of the obituary notice in the *Medical Times and Gazette* in 1860 when his body, still warm, was laid to rest near the priory of Lanercost, where his father had been the owner of Banks House.

During his period of private practice in London, Addison's principal interest had been Dermatology. This was fortunate since later it focussed his attention upon the dark pigmentation of adrenal patients. In Guy's Hospital, Addison supervised the preparation of fine clay models of pathological areas which are still the pride of that institution. In the years which preceded his epoch-making monograph on adrenal lesions, Addison published several works of clinical interest, among which must be mentioned the *Elements of the Practice of Medicine* written with Richard Bright and which contains an excellent description of appendicitis and other clinical descriptions unsurpassed even today; a report, *On the Pathology of Phthisis* (1845), in which he differentiated lobar pneumonic inflammation from the tubercular process as such and which was inspired by his great admiration for Laennec. Addison modified the older concept of Laennec concerning the destructive process of consumption of the lungs and described the *xantoma diabetorum*, which he called "vitiligoidea," in a work entitled *On a Certain Affection of the Skin: Vitiligoidea: a. Plana. b. Tuberosa.* Perhaps because of the retiring nature of the author, these works did not win the fame they really deserved. And for that very reason, perhaps, when he published the clinical picture which he called *melasma suprarenale*, and which again called

attention to the mysterious little glands that lay enveloped in perirenal fat, his report was "a comet in a starless sky." His contemporaries, who were not gifted with his qualifications or his insight, did not appreciate the importance of his study. To be able to correlate aspects of disease intimately connected with its pathogenesis, it was necessary to have been, as Addison was, a dermatologist, a surgeon, a clinician, and a pathologist. But that did not happen, which is further proof that medical discoveries, especially in Endocrinology and Psychiatry, have to avail themselves of the weapons of experimentation in their struggle against authority and dogmatism.

Addison does not seem to have been discouraged. We know that he continued his clinical research with the same fervor as before. Probably the only thing that interested him when he wrote his valuable report, was carrying out his duty as conscientious clinician and communicating what he had observed in the clinic and the autopsy room, without expecting recognition or applause. As he never had many patients, he could devote a great deal of time to each: he thus proved how much more important it is to study conscientiously a few cases rather than flit superficially over thousands just for the sake of piling up statistics.

Addison was the first to use static electricity in the treatment of spasmodic and convulsive diseases in 1837. In collaboration with John Morgan he wrote the first work in English on the action of poisons on the living organism. Some of his favorite medicines, like the pills that bear his name—calomel, squill and digitalis for dropsy—were widely used in his time, although Addison put so little stock in medication that he frequently forgot to prescribe anything for his patients. This fact is of interest for it reveals not his indifference to the patient as a human being but rather his acceptance of the therapeutic nihilism which was then in fashion among many doctors.

Such an attitude contrasts sharply with his all-absorbing desire to establish an ultra-accurate diagnosis. His scientific virtuosity carried him to unbelievable extremes. Deaf in one ear, he had to walk around the patient's bed many times in order to auscultate him in all positions, and would exhaust the patience of both pupils and friends. Often, after visiting a patient who lived ten miles from London, he would return to his home to reflect on the case. If he felt that there was some point still left in doubt, he would retrace his steps and re-examine the patient to allay his doubts. This inquisitive obstinacy to get an exact diagnosis caused him to spend many hours at patients' bedsides in the hospital and in the autopsy room, comparing his findings in the living patient with the lesions observed in the necropsy. We owe his great discovery to that fortunate curiosity.

His psychological make-up reveals a man tortured by doubts, scruples, and uncertainty, inferiority complexes and frustrations. Along with his timidity, his sternness, his deliberate rejection of worldly pomp, his late marriage at the age of fifty,[9] and his crises of anguish which would force him to go out into the street late at night and seek nocturnal companionship to calm his anxiety, reveal a psychotic personality.

It is possible that Addison compared his personal fate with that of colleagues like Bright, or Gull who was the first to describe myxedema, was knighted and left

a fortune of 344,000 pounds sterling at his death. In contrast to them, Addison lived a sad solitary life. He sought neither honors nor fortune, and was not even made a fellow of the Royal Society, let alone a baronet. His greatest honor was being elected president of the Medical and Chirurgical Society of London. In 1860 he retired from public life and his beloved Guy's Hospital because he was obsessed by the idea that younger doctors coveted his post. He went to live in Brighton, the proverbial retirement place of his time, which Samuel Johnson had praised as the "most ideal spot in the world." There, despite the fact that he was watched by two nurses, he took his own life by jumping out of the window.

The period during which he earned his glory comprises the six years between 1849, when his original report on the syndrome of adrenal insufficiency appeared (*London Med. Gaz.* XLIII, p. 517), and 1855 when, urged by his friend the surgeon John Hilton, by his disciples and especially by Samuel Wilks who would later be the compiler of his work, he published his authoritative clinical monograph on the constitutional and local effects of lesions of the adrenal capsules.[10]

In his monograph, Addison described eleven cases of lassitude, bronze-colored skin pigmentation, loss of weight and death, in which necropsy invariably revealed a bilateral destruction of the suprarenal capsules, to which Addison attributed the disease, suggesting that they mainly influenced the red blood-cells. In his description he confused two different diseases: pernicious anemia, today called the Addison-Biermer disease, and the affliction that was later called Addison's disease. In addition to these two diseases, keloid or localized sclerodermia also bears his name. It is a strange paradox that this humble, timid man, who felt defeated in his greatest ambitions, should, after death, have had his name immortalized in three medical eponyms and have opened a radiant path leading to early Endocrinology.

His monograph was the last of the eleven works which Addison published and signed with his own name and were compiled by his disciple Wilks. Nothing more, nothing less. His work gains in scientific quality what it lacks in quantity.

In his monograph, Addison differentiates between the anemias in which no organic lesion can be detected and which later would be called pernicious, and the anemias associated with bronze-colored pigmentation of the skin and lesions of the suprarenal capsules. His little book is *in quarto* and contains only eleven cases, of which those in which only one suprarenal capsule was lesioned have been questioned. Sir Samuel Wilks accepted only four of those eleven cases. This indicates once again that, in the history of Endocrinology, observation and intuition of a few patients, rather than many, has been the basis of great discoveries. Although it is not our purpose to disclaim the ever-growing importance of statistics, we must insist that if our modern methods of statistics had been applied to the analysis of the earliest endocrine cases, it would have resulted in the immediate inhibition of some of the most important scientific discoveries. The history of the knowledge of the adrenal gland has proved that the thorough study of a single clinical case, such as performed by Addison, can provide the necessary key, in Endocrinology as well as in Psychiatry, that opens a new door to scientific investigation.

VII. CRITICAL ANALYSIS OF ADDISON'S MONOGRAPH

Addison's monograph, which raised its author above the three other clinicians and anatomopathologists (Richard Bright, William Gull and Samuel Wilks) who along with him were the "four greats" of Guy's Hospital,[11] was a little brochure of 46 large-type pages richly illustrated with lithographs in color. Let us analyze its importance in the light of the state of medical science in Addison's time.

First, the title: *On the Constitutional and Local Effects of Diseases of the Suprarenal Capsules*. Addison did not give a timid or hesitant title to his work. He decisively established an endocrine etiological implication. For the first time in the history of Medicine a physician took the revolutionary step from the purely morphological to the clinical stage in Endocrinology. Without the help of laboratory facilities, Addison showed how much the clinician can do by using a neohippocratic method of observation—as Pasteur showed in Bacteriology—and the importance of describing and correlating with clarity and concision the discoveries made in the clinic and the necropsy room.

In the second place, Addison described not one but two new diseases, since he revealed pernicious anemia—for which he found no explanation on the autopsy table—by way of introduction to the fundamental theme of his work. In his search for new cases of the disease which preoccupied him, he "stumbled upon" another discovery of greater importance, to which he devoted his monograph. It is quite possible that at first both diseases appeared to Addison identical since anemia, lassitude and death were common to both; but when he published his little book he already clearly understood that they were different diseases, and his purpose was to describe what he called "bronzed skin," or "melasma suprarenale," which is altogether different from the "idiopathic anemia" he describes in his introduction. His clinical description of both diseases is so perfect that even today, a century later, there is no need to add anything except some symptoms obtained with instruments which did not exist in his time. Sir Henry Dale said that if Addison had examined the bone marrow of the corpses of patients suffering from idiopathic anemia, he would not have failed to observe its anomalous aspect even macroscopically. In any case, he was the first to describe that type of anemia, the endocrine factors of which, along with its dramatic treatment, have been disclosed not long ago.

In the third place, we must stress the fact that Addison based his discovery on only 11 cases, just as Pierre Marie in 1886 would base his description of acromegalia on 2 cases of his own and 5 reported by others. This proves, as F. G. Young pointed out, that "*the world of biology, and particularly of medicine, rarely displays the mathematical regularity and platonic perfection that allow a statistician to assess the significance of the result of the small number of observations that alone are often impossible.*"

We must bear in mind that Addison's work was carried out at the end of an observational period and when the experimental period was about to begin. Forgotten were Harvey's demonstrations that the experimental method might lead to almost anything in Medicine, including the description of the circulation of the blood. English physicians had relegated the experiment to the position of an amuse-

ment for capricious surgeons like Hunter or Bell. Addison did not experiment. It is therefore historically important to emphasize that he went as far as anyone could go relying only on observation at the patient's bedside and in the autopsy room. Experimentation would come later, beginning in the Old World, and it would initiate a new era in Endocrinology. Addison represents the end of two thousand years of observation of the endocrine glands; he is the link between the clinic and pathological anatomy. His is a triumph of observation, but a triumph limited by the natural boundaries of the hippocratic method.

And finally, Addison was the first to emphasize that the nature of the symptoms of adrenal patients—to whom he was first attracted, no doubt, by the bronzed pigmentation of their skin, a carry-over of his first love, Dermatology—does not depend so much on the lesions found in the suprarenal capsules as on an interference in their function.

When Addison made these statements, he was going against the grain of the times, because reflexology—correlation and integration by purely nervous mechanisms—was still fashionable among physicians, and biochemical and endocrine correlations had not yet made their appearance. Nerve coordination had prevented the development of any concept of a humoral regulation and had therefore held back the progress of chemistry.

In a discussion at the *Royal Medical and Chirurgical Society*, Addison said: "*We know that these organs [suprarenal] are situated in the direct vicinity and in contact with the solar plexus and semilunar ganglia, and receive from them a large supply of nerves and, who can tell what influence contact of these diseased organs might have on those great nerve centers and what share that secondary effect might have on the general health and in the production of the symptoms presented?*"

Addison introduced into the study of the adrenal gland the holistic principle which today dominates Endocrinology. Following that principle, the patient is examined clinically in the light of a neohippocratic criterion: he is considered as a whole, and then a detailed examination of his parts is made. Finally, study is made of the relation among the parts in order to arrive at a final synthesis, in which there reappears the totality of the endocrine patient and his disease. Addison's was the dialectical method—introduced by Plato as the supreme road to knowledge, and applied by Hippocrates to Medicine—which proceeded from the knowledge of the whole to a knowledge of the parts and then returned to the whole. Addison was the first to view the hypoadrenal patient as a clinical whole, and then to relate the disease to the disturbance of one of the diseased organs: the adrenal glands.

Addison initiated the clinical and physiological phase in the history of the adrenal glands.

VIII. THE EXPERIMENTS OF BROWN-SÉQUARD: THE PHYSIOLOGICAL STAGE

The next stage in the history of our knowledge of the adrenal glands started across the channel from England, on continental soil. In England, the experimental method in Medicine had been gradually abandoned. But in France, the naturalistic and experimental method enjoyed a new renaissance, manifest not only in Medicine but

especially in Art, Literature, and Philosophy. For it seems that the great medical movements throughout the centuries have followed the evolution of the dominant philosophical tendencies; they have been epicycles linked, like beads on a necklace, to the development of the great historical processes.

In the second half of the XIXth century, men of science in France and other European countries, as well as men of letters, were drawn into the vortex of "naturalism." *Fin de siècle* novels became ill-disguised clinical histories and had their counterpart in a wave of experimentation in European medicine. Physiology appeared to European minds to be the most philosophical of sciences because its objective was to investigate the functions of life.

The new physiological phase in the history of our understanding of the adrenal glands began in France in the wake of a report made by Trousseau, who suggested that the "bronzed disease" be called "Addison's disease." In this paper, Trousseau criticized some of the methods of Brown-Séquard; he said that these methods had to do with examination of animals, whereas the problem was mainly of a clinical nature. Once more the clinician and the physiologist clashed in the scientific ring without realizing that they were both dealing with the same problem but from different vantage points.

When Addison published his monograph in 1855, Charles Edouard Brown-Séquard, the passionate research scientist whose romantic life and dazzling experiments in the field of nerve physiology had earned him world-renown, was a man of 38 with a restless mind constantly looking for new scientific fields to conquer.[12] When Brown-Séquard read of the effect which, according to Addison, adrenal lesions had on the human being, he immediately tried to reproduce this effect experimentally. In that way he took the decisive step—from observation of the disease to its experimental reproduction—in endocrinological research. In his laboratory, Brown-Séquard removed the adrenals from 51 rabbits, 11 pigs, dogs, cats and rats, and observed that all of them died after twelve hours. When we try to interpret the experiments of Brown-Séquard historically, we see that what he set himself to do (he was not a clinician but a physiologist for whom the animal in the laboratory and not the patient in the clinic was the working tool and the object of examination) was to show that these neglected organs played an all-important role in the life of mammals. He himself was perhaps unable to appreciate fully the tremendous significance that his discovery would have in Endocrinology.

In his epoch-making report, presented to the Academy of Sciences in Paris on August 25, 1856, Brown-Séquard pointed out that the symptoms observed after removal of the adrenal glands were progressive muscular debilitation, accelerated, irregular and gasping respiration, debilitation and acceleration of the heart beat, dizziness, and convulsions. If the blood of a healthy animal was injected into the veins of an animal without adrenals, the latter lived a few hours longer. Brown-Séquard was convinced that the cause of death had not been hemorrhage, peritonitis, lesions of the surrounding organs, nor interferences with the fibers which the great sympathetic nerve sends to the adrenals. The blood of adrenalectomized animals was probably charged with a toxic principle, since when an animal with only one

adrenal was injected, his death was speeded up. The final conclusions were that those organs were essential for the life of dogs, cats, rabbits and guinea pigs; that their removal produced death more rapidly than the removal of both kidneys, and that they were intimately related with the cerebrospinal centers.

Brown-Séquard presented three papers to the *Académie de Sciences*, in which he summarized eight months of work on the adrenals of laboratory animals. To what has been mentioned above he added that, contrary to the then prevalent opinion, the suprarenal "capsules" were not simply embryonic structures, but that in man and in animals they increased in size from birth to maturity. He also affirmed that their removal caused the death of the animal because there existed in the blood a toxic principle which the adrenals could no longer neutralize, or because they gave to the blood a "disintoxicating" property which disappeared with their removal. In addition, he pointed out the strange parallel which existed between the rabbits which were then dying in Paris from a certain fatal epizootia—and showed symptoms analogous to those of adrenalectomized rabbits, presenting an inflammation of the adrenals in autopsy—and patients suffering from Addison's disease.

Brown-Séquard's work was a milestone in the history of Endocrinology; it initiated the physiological and experimental stage in the investigation of the adrenal gland, and established the latter's "antitoxic function." This concept would be extended to the other endocrine glands during that stage in the evolution of Endocrinology which I shall later call "antitoxic." Brown-Séquard was so impressed by the results obtained, that from then on his individual philosophy seemed to change. He, who had been up to then a pure physiologist, became an applied physiologist.

As was to be expected, Brown-Séquard's colleagues criticized his work—for in Medicine most innovations have been criticized owing to routine, inertia, and envy. Trousseau, faithful to his clinical education, insisted that he had examined a case of Addison's disease; after autopsy he had sent Brown-Séquard the adrenals of the patient so that he might examine them under the microscope. Brown-Séquard found in them tubercular deposits, a "cretaceous material," a humor-like pus, and very few leucocytes, which confirmed Trousseau's findings and connected the hospital and laboratory in a harmonious synthesis.

To the criticisms of his colleague Bouillard, who called Brown-Séquard's experiments an "amusing sort of physiology," the latter answered with great dignity that criticism of his work was "a negation of the value of a great scientific method." He thus broke a lance in the cause of the experimental method in endocrinological research.

Brown-Séquard was a pioneer in Endocrinology; although he probably knew only superficially the speculations of Théophile de Bordeu,[12] he broadened the conception of the existence of an internal secretion in the glands without an excretor duct, thus anticipating neurohumoralism on the basis not only of experimentation but also of imagination.

The major criticism that can be directed at his experiments is that Philippeaux in 1857 showed that it was possible to remove the adrenals in rats and yet to keep them alive for many months; Philippeaux explained that the deaths observed by

Brown-Séquard were a result of traumatic lesions of the tissues, especially the sympathetic nerves, contiguous to the adrenals. It is probable that many of the deaths during experiment were caused by traumatic shock and sepsis, since those deaths which, according to Brown-Séquard, were caused by removal of a single adrenal gland were later, when a good surgical technique was used, shown *to be due* to other causes. Tizzoni (1886), Abelous and Langlois (1891) confirmed the fatal effect of double adrenalectomy. Whatever it was that produced the result of Brown-Séquard's experiments, his conception was physiologically correct and biologically of extraordinary brilliance.[14]

Brown-Séquard's contribution to the knowledge of the adrenals was completed on June 1, 1899—another memorable date in the history of Endocrinology—when the famous physiologist presented to the *Société de Biologie* of Paris a paper on autorejuvenation. Although the quantities of testosterone which he injected into himself could not exercise a notable effect except psychologically, his thesis on the mechanism of endocrine integration, independently of nervous integration, established the bases of modern Endocrinology.

"*We admit*," Brown-Séquard said on that occasion, "*that each tissue, and more generally each cell of the organism, secretes for its own account products or special ferments which are poured into the blood and which come to influence, through the mediation of this liquid, all other cells which are thus separated one from the other by a mechanism other than that of the nervous system.*"

If Addison made the first clinical interpretation of the role played by the adrenals, Brown-Séquard represents the beginning of experimental and physiological research into these organs. With him begins the "antitoxic" stage in the history of the "concept" of the adrenal glands, an interpretation which was abandoned later but which has been revived in Selye's investigations into the "defensive" role of the adrenals. All of which once again indicates the eternal *ritornello* of medical theories in the unrolling panorama of History.

IX. FROM THE ADRENAL ANATOMY TO ITS FUNCTIONS

Suddenly the concept of the adrenals takes a gigantic step forward. Instead of going ahead with the study of the anatomy of the adrenal glands, research scientists proceed to the study of their secretion. Interest no longer centers around the organ, but around its functions.

As the XIXth century drew to a close, technical progress stimulated interest in the problems of Physics and Chemistry. Research, aided by new instruments and a new conception of Science, buttressed the work done in laboratories and eased out philosophy. The result was that men of science began to make notable progress in the field of organic chemistry. The study of internal secretions gradually took the place of anatomical study of the endocrine glands.

We cannot consider this stage, in which facts are more important then men, without rapidly enumerating the series of links which led to the discovery of adrenal hormones and prepared the way for what we may call the metabolic stage in the history we are sketching.

In 1856, Vulpian, a physician at la Salpetrière, had discovered that in the adrenals the cells of the medulla differ from the corticals by their color—only the medulla acquires a green tint in a solution of ferric chloride—and in the blood which comes from them he discovered a chromogene related to the secretion of these glands. Henle, in 1865, observed that certain granules of the medulla cells give a cloudy red precipitate—the chromafine reaction—with diluted solutions of potassium bichromate.

Perhaps the most important historical factor in the trend to study internal secretions chemically was a new interest in therapeutics, that neglected branch of Medicine. Until the early part of the XIXth century, therapeutics was in the same state it had been 1500 years earlier; that is, it was based on the idea that illness was something foreign to the body which had to be expelled, a belief which made for a therapy of the eliminative type. Diuretics, emetics, diaphoretics, laxatives, and blood-letting "scientifically" replaced the ancient exorcisms to expel the demons from the body of the patient, although essentially it all sprang from the same philosophical process: to eject demons, miasmas, or germs from the body, a carry-over from the conception of disease as the possession of the patient by a foreign influence. At the beginning of the XIXth century, new diagnostic methods of auscultation and percussion accentuated interest in diagnosis but weakened development in therapeutics. At the end of the last century, fresh information on Immunology and Endocrinology awakened a universal medical interest in therapeutics, which led to a passionate search for serums, vaccines and hormones comparable only to the relentless drive of the medieval alchemists to find the philosopher's stone.

X. THE FIRST ACTIVE ADRENAL EXTRACT: THE METABOLIC STAGE

Forty years after Addison's great accomplishments, the adrenal glands seemed to have fallen into the dust of oblivion. This fact contrasted with the impressive cavalcade of clinical and physiological discoveries which were leading to the integration of a set of ideas concerning internal secretions. Because of technical difficulties, the adrenals were set aside and the progress of scientific knowledge about them interrupted. The idea that Addison's disease was a sort of "autointoxication" because of an "insufficiency of adrenal excretion" still prevailed. Under these circumstances, two English physicians made a contribution which marked the next milestone in the history of Endocrinology: the discovery of an active adrenal extract.

In the summer of 1894, there was practicing in the English town of Harrogate a physician by the name of George Oliver, who was interested in the measurement of pulse rate and blood pressure in man. Oliver observed with amazement the beneficial effect produced when he injected into patients suffering from hypertension watery extracts from the adrenals which *raised* their blood pressure. He then decided to investigate the influence of the injection of these extracts into his own son. When he observed a contraction of the radial artery, he decided to consult his friend Professor E. A. Schafer, of the University College of London. His incredulous friend gave this extract to an anaesthetized dog in which he had been measuring blood pressure, and noticed with great surprise that the little column of mercury rose until

it almost burst out of the tube. That was unheard of, since all the work done up to then with tissue extracts had revealed that the latter *lowered* blood pressure.

Later studies revealed that that active principle was not produced in the cortex but in the adrenal medulla,[15] and that, when injected into animals whose adrenals had been removed, it did not relieve the aforementioned symptoms. They thus arrived at the important conclusion that the adrenal was a gland with two anatomical parts performing two distinct functions, that the medulla produced a principle capable of *increasing* blood pressure, and that the cortex might be producing other vitally important secretions. These experiments (1894–95) paved the royal road which led Abel in 1899 to isolating the adrenal (medullar) active principle in the form of insoluble benzoilate; it also led Furth (1897–1903) to obtain amorphous compounds purified to the highest degree from Abel's "epinefrine"; and finally it led Takamine and Aldrich—independently of each other—to obtain in 1901 a pure crystalline compound of natural levo-adrenalin which was called "suprarenin" by Furth and "adrenalin" by Takamine.[16]

The importance of the discoveries of Oliver and Schafer lies not only in the fact that they led to the isolation of a hormone for the first time, but also in the fact that they opened a path to new conceptions concerning endocrine dynamics. These were the beginnings of the confirmation of the law that the pathological importance of an organ is the function of its physiological importance, and the physiological complexity of the adrenals indicated their vital importance. When it was perceived that multiple tissues and different secretions existed in this gland, thought was also given to the multiplicity of its physiological functions. Today we know that the functional and hormonal division of the adrenals corresponds, to a certain degree, to the clear division of its cortical or epithelioid tissues and the medulla or nervous and chromafine tissues. It has even been said that the adrenal is made up of two different glands wrapped up in the same capsule. That there is a great deal of truth in this assertion has been proved, because from that point on in the evolution of our knowledge of the adrenals it has been necessary to consider separately the the adrenal medulla and cortex, the physiological and philosophical synthesis of which is again—but only partially—being carried out today.

In 1905, Stolz and Dakin simultaneously prepared a racemic adrenalin. Friedman established in 1906 the structural formula of the hormone. Flacher obtained in 1908 two optic isomers from this formula. Thus for the first time—the history of the adrenals is crammed full of facts which happen for the first time in Endocrinology—a pure crystalline hormone was obtained, isolated, and synthetized. The concept of the adrenal function had crossed another decisive threshold: it was possible to reproduce in the laboratory the natural hormone in which lay the mysterious adrenal function.

XI. TECHNICAL PROGRESS CONTINUES: THE LABORATORY AND THE CLINIC

For years—since Stockman in 1867 had made the first fruitless attempts at adrenal hormonotherapy—scientists had been using adrenal glandular products of a varied nature obtained through different and rather rudimentary techniques, such as the

entire gland fresh and dessicated, and dry glycerinated extracts, applied through different organic channels. In 1903 Adams published a statistical report of 97 cases treated with these extracts which, because they contained marrow, produced, in the main, an elevation of blood-pressure: quite a few patients improved under this therapy. In 1904, Raven used pure adrenalinic hormone on a patient suffering from Addison's disease, and for the next fifteen or twenty years this was the principal therapy for this disease; when associated with total extracts and general tonics this therapy brought about a rise in the number surviving that mysterious illness. The case cited most often in medical literature was that of Muirhead, professor of Pharmacology, who diagnosed and treated himself successfully with large quantities of adrenalin and total adrenal glandular extracts, initiating a phase in this therapy.

A revolutionary advance then took place in the techniques used during this historical stage in the chemical investigation of the adrenals.

For many years, all active endocrine extracts—including the original preparation of insulin by Bantin and Best—had been obtained by aqueous extraction starting from the glandular tissue. In 1927 Rogoff and Stewart reported that they had prepared unpurified adrenal saline extracts which were active in prolonging the lives of adrenalectomized animals, but this was not quite confirmed. Two other scientists, Swingle and Pfiffner, eighty years after Addison's description, had the brilliant idea of extracting adrenal tissue with alcohol after breaking it up with several types of lipid solvents including benzene, and injecting it in oil suspension. These extracts were found to prolong the life of adrenalectomized animals and they were pure enough not to cause abcesses. Today this method of extraction with lipid solvents is still the basis for the industrial manufacture of these hormones. The success of these scientists is due—according to Young—to the following facts: they used an enormous amount of experimentation material (350 cats in the preliminary experiments); they saw that aqueous adrenal extracts might contain a certain quantity of adrenalin, which made them dangerous and toxic if given in great quantities; they used fatty dissolvents for a gland as rich in lipids as the adrenal cortex, and, on the basis of the great amount of cholesterol in the blood, they destroyed the point of view that a hormone cannot have the structure of a lipid; they also administered enormous—hyperphysiological—quantities of the extract. As Vogt pointed out (1950), normal adrenal secretion would exhaust in 6 to 12 seconds its stored-up active material since it is evident that this gland stores up very little of the hormone in a form capable of being extracted. Later, Swingle and Pfiffner also described a method of extraction in aqueous solution, and another method for eliminating the adrenalin by filtering it through permutite which utilized the interexchange of ions for biological purposes.

The laboratory, in happy conjunction with the clinic, thus brought to a close another stage in the historic evolution of the concept of the adrenal function.

XII. HORMONES AND NERVE FIBERS: NEW ORGANIC CORRELATIONS

The next stage would be of enormous biologico-philosophical importance in the evolution of the concept of adrenal hormones.

Up to then the notion that had been taking shape as a result of years of research and theorizing, had been that the hormones in general were chemical messengers transporting physiological orders through the blood to the different organs of our body. By one of those brusque shifts so frequent in History, the pendulum swung radically from the concept of organic regulation by the nervous system to the concept that this function was carried on by internal secretions. The following events showed that this organic regulation is not exercised unilaterally by the hormones, but that it is a function both of the hormones and the nervous system.

In 1902 Lewandowsky and Langley showed that a notable similarity existed between the action of adrenal extracts and the result of the stimulation of the sympathetic nerves. Two years later, Elliot made the same observation, using adrenalin this time and propounding the hypothesis that adrenalin might be the chemical excitant which is liberated when the sympathetic nerve impulse reaches the periphery at the level of its nerve endings. In 1921, Loewi showed that by making a Ringer solution circulate through a heart removed from a frog, the solution may acquire sympatheticomimetic properties (and increase the frequency and amplitude of the cardiac contractions when applied to another heart) if the sympathetic fibers of the vagosympathetic nerve[17] are stimulated. This *Acceleransstoff* or Loewi's accelerating substance, hypothetically liberated during sympathetic stimulation, was later (1931) called *sympatine* by Cannon and his collaborators, and it was shown that stimulation of the sympathetic nerve liberates a substance in the nerve endings of the organs innervated by fibers called adrenergical because they imitate the adrenalinic effect. And so another new concept was introduced into Endocrinology: that the effects of all nerve impulses emanating from peripheric nerves are caused by the liberation of certain chemical substances.

Doubt about whether the transmitting adrenergic substance was always and totally adrenalin was allayed years later when Cannon dubbed it "sympatine." It was thus established that the effects of adrenalin, when applied artificially are similar but not absolutely identical to the effects of the sympathetic nerve impulses and the chemical transmitter which is released into the blood—at the point where the endocrine gland which produces it liberates it—to be carried a great distance.[18]

The endocrine function of the adrenal medulla, as Cannon would show, was thought to strengthen the actions of the sympathetic nerves in emergencies, in sudden requirements of activity, or in cases of emotional tension, and that its hormone or adrenalin was the peripheric transmitter of the adrenergic impulses. At first, it was thought that the lack of this hormone from the adrenal medulla played an important part in Addison's disease. Afterwards it was discovered that the principal symptoms of this disease—weakness and languor, muscular asthenia, high blood-pressure, alterations of the normal balance of inorganic salts in the humors and organic tissues, disposition to attacks of hypoglycemia, and general lack of normal resistance to infections and intoxications, thermic changes and other influences, and its fatal end—are always or almost always contingent upon the lack of hormones produced by the adrenal cortex, the collapse of a vast endocrine arch of functional structures the keystone of which is the adrenal cortex.

This article will be continued in the December issue

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Symptomatology of Stuttering

*Elly Sittig**

NEW YORK, N. Y.

The following description of the symptomatology of stuttering is based upon Dr. Emil Froeschels' experience with more than 16,000 cases.†

There is only one type of sign present at the onset (provided that the stuttering has not been caused by severe injury), which consists of repetitions of syllables and short words. It is now generally accepted that iterations are as a rule the initial sign.**

It must be emphasized that initial iterations are characterized by a normal speed measured against that part of the patient's speech which progresses normally. In this period of stuttering, no disturbance of the normal breathing, no accompanying movements, no signs of phobia are present. The iterations represent, at least at the very start, a kind of "filler" for missing words, or for words the meaning of which is not entirely clear in the mind of the child. Such difficulties in the finding of words or word forms in time seem to be most characteristic of that period in which the child, driven by an inner impulse, must acquire the skill of forming phrases, the skill of mastering grammar, and syntax.

As this phase develops between the ages of about 3–5 years, stuttering starts most frequently at this time (never at the time when the infant makes first attempts at talking, proving therefore, that it is not congenital). Eighty per cent of all children go through a period of frequent or rare repetitions; vivacious and intelligent children particularly go through this stage of iterations. The "speech temperament" and the ability to find words quickly are somehow incongruous in such cases. The first iterations are nothing but the result of a vacuum in the speech engine. Normally, congruity between the speech temperament and the word-finding capacity is established within a few months. A spontaneous cessation of the repetitions in a majority

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†Emil Froeschels: "Pathology and Therapy of Stuttering." The Nervous Child, vol. 2, no. 2, January, 1943.

**Wendell Johnson: J. Speech Disorders, vol. 7, no. 3, 1942.

The *International Record of Medicine* takes pleasure in opening with this issue a new section, representing the continuation of the *Pan American Medical Woman's Journal*. In this section articles, reports, and news will be published concerning the activities of medical women engaged in research, medical practice and teaching in the Western Hemisphere.

of cases can be therefore expected. In only about 2 per cent do they persist, become fixed as a neurotic symptom, and, sooner or later, are accompanied by other signs. In some cases the iterations obviously become habitual, as the patient is not lacking in vocabulary. Sometimes the repetitions persist throughout life, while no other abnormal signs appear. Such cases never achieve the congruity between speech temperament and the capacity of word-finding. They form the group of clutterers.

Dr. Froeschels has found that the other signs which in more advanced stages often accompany iterations, follow a certain order of appearance. In other words, not all of them emerge at the same time. But when they do appear, the signs already present do not vanish, but persist concomitantly with the more recent ones.

Sooner or later the iterations are complicated by a pressure in those muscles of the speech apparatus that are engaged in the formation of the first sounds subject to repetitions; e.g., ba-ba-ba is no longer spoken in a normal tempo, but the lips are closed firmly when the b's are pronounced. This procedure is delay. If we term the iterations "clonus" and the pressure "tonus," then the combination of the two may be called "clonotonus" and "tonoclonus," respectively, depending on which sign is more prominent. It seems evident that the tonic component is due to an attempt on the part of the child to overcome the iterations, an attempt that obviously misses its aim.

A child's attention may be drawn to his iterations by persons in his environment, by chance, or by a kind of hypochondriac self-observation. Frequently both parents and nurses ask the child to repeat the "difficult word," or to speak slowly, or to avoid repetitions, or even to take a deep breath. If they knew the real source of those iterations, they would try to enrich his vocabulary or his skill in forming phrases by telling stories and by asking him to repeat sentence after sentence. By advising the child to repeat the "difficult word," etc., they lead him on the wrong track. He begins to think that there are difficult words, or even that a forceful pronunciation may help him. Self-observations may bring him to identical conclusions. The result will be a phobic attitude toward speech and tonic components.

If clonotonus and tonoclonus arise, then breathing must begin to show abnormalities, since air cannot escape during the blockage. Blushing and grimaces as well as reflex contractions of muscles remote from the mouth may appear. Habitually, in the development of this form of stuttering, these "accompanying movements" do not appear before the tonic component is present.

Clonotoni and tonocloni naturally delay the flow of speech and therefore we call them slow clonotoni and slow tonocloni. (As will be shown later, fast tonocloni and fast clonotoni are also among the signs of more advanced stages of stuttering, but they are due to a long "training" and are, therefore, later signs.) Sometimes a single sound is produced clonotonically or tonoclonically and even that in a fast tempo ("Rothe clonus" named after Dr. Froeschels' late collaborator, Rothe).

In some children an early sign consists in the drawling of vowels. Others refuse to speak—they become mute for weeks, or else they speak in a whisper.

The tonic component comes more and more in the foreground, until the pure tonus results in a blockage, without repetitions, in the muscles of the larynx, the pharynx, or the mouth. Either one or several of these muscles may be overcontracted at a

given time. Accompanying movements and different kinds of breathing trouble are usually associated with pure toni. These toni remain slow for years.

The accompanying movements, starting probably involuntarily, are apt to distract the attention of the patient from the "difficult word." Since this *attention* is the only *cause* of the blockages, speech proceeds fluently at such a moment. Many patients therefore believe that accompanying movements are an aid, and consequently some of them use these movements deliberately. Since the latter lose suggestive power after a time, other accompanying movements are invented by the patient to replace them. A peculiar type of movement of this kind are "embolophrasias," consisting of the use of sounds, syllables, or words as "starters." It is evident that embolophrasias, although they may become automatic at later stages, are intentional aids. Their connection with the will is not to be doubted.

But there is another proof of the participation of the patient's will in the whole stuttering complex. All the accompanying movements can be of the clonic as well as of the tonic form, with one single exception. This exception concerns the external muscles of the eyeballs. A few examples may make clear what is meant by the conception of a "tonic" or a "clonic" accompanying movement. One patient shakes his head, looks upward, clenches his fists. In another moment he may shake his fists, blink, bend his neck, turn his eyeballs to one side, stamp, and say "bla-bla," before he actually begins speaking. Shaking, blinking, and repeated "starters" are examples of the clonic, the other accompanying movements of the tonic form. Long experience has proven that all voluntary muscles can "accompany" stuttering clonically, as well as tonically, except the external muscles of the eyeballs. Stutterers may look up, down, or to the right or left during an attack of speech difficulty, but vacillation of the eyeballs never appears as a stuttering symptom. This vacillation is known as nystagmus, and will never accompany a stuttering attack, provided that it has not been previously present in form of spontaneous nystagmus, nystagmus due to a labyrinth affection, or nystagmus of the optic type.

If we search for the reason of this striking difference between all the other voluntary muscles and the external muscles of the eyeballs, we can offer but one explanation: the other groups of voluntary muscles can voluntarily produce "tonic" and "clonic" movements (e.g., bending and shaking of the head), but the external muscles of the eyes can voluntarily produce only the tonic form. Nobody is able to create nystagmus at will, since it is a pure reflex. Though the conclusion drawn pertains to the nature of stuttering, it seems that this much should be stated here in order to facilitate understanding of the symptomatology. All abnormal movements involved in stuttering are somehow related to the will; they are not real cramps, but cramplike movements.

The further development shows variations in the tempo of the signs so far described. The tonoclonі as well as the toni may become accelerated instead of slow, and so may the simple clonі. For instance a patient who for years has said "goo-goo-good day" pronouncing the repetitions at the speed of his normal speech may say "goo-goo-good" very fast or very slowly. It seems as though he has used up, at least temporarily, the aid that the primary clonі offered to him.

The voices of stutterers in advanced stages are frequently soft and monotonous. Sometimes the voice is blocked (tonus of the laryngeal muscles) or reacts clonically. Speaking during inhalation is a frequent occurrence in advanced stages.

Sooner or later the surface picture of stuttering changes from more obvious signs to less dramatic ones. For instance, a patient who has made grimaces, stamped his feet, and pushed his trunk back violently, may later merely look upward and stare, motionless, before he begins to speak. This phase is called "concealed" stuttering.

Advanced cases frequently avoid difficult words by substituting other words, or by changing the position of the troublesome words in a sentence (because they often have proved difficult only in the neighborhood of certain other words). Sometimes patients prefer not to speak at all.

We can now return to the development of the signs of stuttering, beginning with syllable repetitions and ending with the stage of hiding. It seems that the progress from one sign to the next is due to an *inner logic* (Froeschels). At its beginning, the tonic component represents an attempt at overcoming the iterations. The accompanying movements, distracting the attention from the blocking speech muscles, are regarded as aids by the patients, and are later used as such. When older signs lose their effectiveness in overcoming imaginary difficulties, they are partly replaced by new inventions. These consist only of modifications of speed, *because the patient considers strength of the muscle contraction as the inevitable factor in the original difficulty*. Rapid tonocloni, rapid toni, rapid cloni, and slow cloni are the remaining possibilities that the patient will exploit as new aids. The hiding stage finally is another invention, for "beautifying" purposes.

This classification has also proven a means of differentiating the form of stuttering of specific origin, namely, stuttering acquired by imitation. This form could previously not be diagnosed unless the case history could be obtained. And those histories have not always proved reliable.

It is the absence of the inner logic that makes a case suspect of being one of "imitation stuttering." Imitators prolong the closure of the lips, or the articulation of the tongue with the palate, or any other form of articulation, but when they open their mouths, no violent articulation is to be seen, and the skilled ear does not hear the strong explosion expected. (These are also the mistakes always made by actors who play the role of a stutterer, and by people telling "stutterer" jokes.)

This form of tonic components in a tonoclonus, or the form of a tonus consisting in an inadequate degree of muscle contraction in relation to the duration of the stoppage, may be called untrue tonoclonus or tonus, respectively. Untrue tonocloni may also result from a treatment that, without being successful, has nevertheless influenced the patient sufficiently to diminish the overcontractions of the muscles. If the stoppages nevertheless persist, there will be untrue tonic components and untrue toni.

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FOREWORD

The QUARTERLY REVIEW OF MEDICINE is devoted to the presentation of selected abstracts encompassing the various subdivisions and related fields of internal medicine. Not only the content but the status of the material in its relationship to present-day knowledge and concept influences the basis of selection. Special review articles and advanced experimental and clinical reports on the subjects of current interest are also included. It is hoped that noteworthy trends in the field of internal medicine will thus be recorded and a proper perspective on the rapidly changing and dynamic state of medical knowledge attained.

The abstracts and editorial comments are grouped together under the following headings:

INFECTIOUS DISEASES
ONCOLOGY
RESPIRATORY DISEASES
CARDIOVASCULAR DISEASES
GASTROINTESTINAL DISEASES
GENITOURINARY DISEASES
MUSCULOSKELETAL DISEASES
NEUROLOGY AND PSYCHIATRY
HEMATOPOIETIC DISEASES
ALLERGY
METABOLIC AND ENDOCRINE DISORDERS
GERIATRICS
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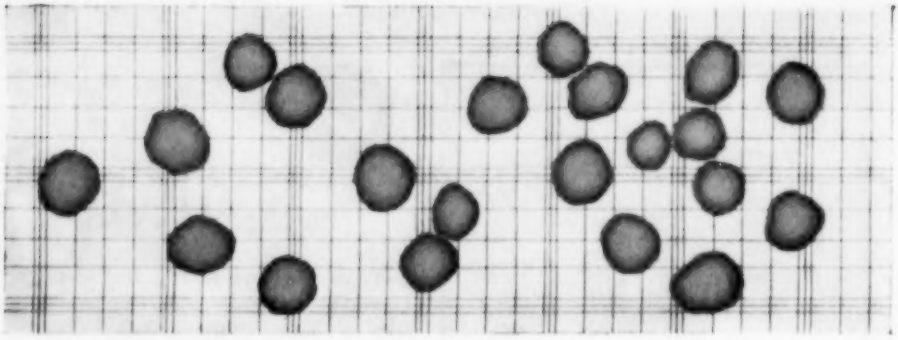

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Quarterly Review of **MEDICINE**

VOLUME 9 NO. 4 **NOVEMBER 1952**

Incorporating the International Record of Medicine

Emanuel B. Schoenbach

1911–1952

On Saturday, September 6th, Emanuel B. Schoenbach, Editor-in-Chief of the *Quarterly Review of Medicine*, died of a heart attack at his home in Brooklyn. For the Washington Institute of Medicine this was a particularly unexpected loss, since Dr. Schoenbach had only directed the Editorial Board of that magazine since the beginning of 1952, and in every other phase of his activity, at the age of 40, was just starting on an extremely promising career. His capability as an Editor was fully demonstrated by his own highly informative scientific contributions, his appointment of an active and able Editorial Board, and his skillful editing and rewriting of all material for that journal.

Emanuel B. Schoenbach

A research expert in bacteriology and chemotherapy of infectious diseases, Dr. Schoenbach was engaged in research on the chemotherapy of cancer at the time of his death. He had been Professor of Medicine at the State University Medical Center at New York and Director of Medical Services at the Maimonides Hospital of Brooklyn since September 1951. Two years ago, while he was Associate Professor of Preventive Medicine and Assistant Professor of Medicine at Johns Hopkins Medical School, he took part in studies which developed a compound that helped to starve cancer cells. Two months before his death, the American Cancer Society announced that he had found an apparent remedy for the usually fatal fungus infection, blastomycosis.

ABSTRACTS

INFECTIOUS DISEASES

176. *Priscoline in Acute Poliomyelitis. Clinical Observation of Seventy-one Patients.* A. C. LA BOCCETTA AND K. E. DAWSON, Philadelphia, Pa. J. A. M. A. *148*: 1083–85, Mar. 29, 1952.

There is clinical evidence to show that, in some patients with acute poliomyelitis, pain and spasm are the result of ischemia from angiospasm which can be relieved by increasing the blood supply to the muscles with external heat or vasodilator drugs. Priscoline (R) (2-benzyl-4, 5-imidazoline hydrochloride), a sympatholytic drug, has been found effective by Smith and associates to relieve pain in patients with poliomyelitis. Seventy-one patients with acute anterior poliomyelitis were treated with Priscoline (R) in the Philadelphia Hospital for Contagious Diseases in 1950. These included 4 nonparalytic, 1 bulbospinal encephalitic, 1 spinal encephalitic and 65 with spinal involvement. Of these patients, 45 had spontaneous muscle pain, 24 had pain on motion or with muscle stretching, and 2 had spasm without pain. Twenty-three of the patients were from birth to four years of age, 26 were from five to nine years. Priscoline (R) was given intramuscularly initially to determine the effectiveness of the drug. The intramuscular dose of Priscoline (R) for patients from 1 to 15 years of age was from 25 to 50 mg., and over 15 years from 50 to 75 mg.; the oral dose was 50 per cent larger. The dose of Priscoline (R) was increased until there was relief of symptoms or until untoward reactions appeared. Twenty-seven per cent of the patients obtained complete relief of pain and spasm, 37 per cent obtained partial relief, and 37 per cent obtained no relief. Seventeen patients had nausea or emesis, diaphoresis occurred in 7, chills in 6, diarrhea in 1, and palpitation in 1; urticaria occurred in 1 patient in this group. It is recommended that patients with acute anterior poliomyelitis, who have muscle pain and spasm, be given a trial with Priscoline (R).—*Author's abstract.*

177. *Nocardiosis: Three Case Reports.* I. L. BERNSTEIN, Fort Wayne, Ind., J. E. COOK, Iowa City, Iowa, H. PLOTNICK, Dayton, Ohio, AND F. J. TENCZAR, Chicago, Ill. Ann. Med. *38*:852–63, March 1952.

In a review of the literature 43 cases of nocardiosis were found; the authors report 3 new cases, 2 of which were fatal. In the first case in addition to symptoms resembling those of pulmonary tuberculosis, there were multiple subcutaneous abscesses and disorientation. *N. asteroides* was isolated from the pus of the subcutaneous abscess during life, but intensive treatment with antibiotics was unavailing; at autopsy abscesses were found in the cerebral hemispheres. It is noted that this patient had had pulmonary silicosis, a condition not noted in any of the reported cases. In the second case both pulmonary and neurologic symptoms were

noted, the latter suggesting the presence of a brain abscess, which was confirmed at autopsy. Nocardias were not isolated in this case during life, but *N. asteroides* was isolated from the brain abscess as well as from the pleural fluid at autopsy. In the third case, the symptoms resembled those of pulmonary tuberculosis with pleurisy; in this case the Nocardia organisms were isolated by culture from the pleural fluid, but the authors call attention to the fact that the cultures contained acid-fast mycelia that were similar to *Mycobacterium tuberculosis*. In this case combined streptomycin-penicillin therapy resulted in recovery, and the patient has shown no recurrence in four years. In most of the cases of nocardiosis reported sulfadiazine has proved more effective in treatment than the antibiotics. Penicillin has been found to inhibit Nocardia organisms if given in sufficiently large dosage to produce high blood concentrations. In *in vitro* tests streptomycin in high concentration also has been found to inhibit the organisms, but no case, other than the authors' third case, has been reported in which streptomycin-penicillin therapy effected a cure. They advise that sulfadiazine should be included in combined therapy for nocardiosis and that other drugs should be evaluated for therapy by *in vitro* sensitivity tests. 21 references. 8 figures.

178. *Clinical Experience with Streptokinase and Streptodornase in Tuberculosis.* JOSEPH M. MILLER, PERRIN H. LONG, AND EDWARD S. STAFFORD, Baltimore, Md. J. A. M. A. *148*:1485–89, April 1952.

Streptokinase and Streptodornase are surface-acting compounds, producing a selective chemical debridement of infected wounds. Streptokinase causes the liquefaction of fibrin, and Streptodornase causes the hydrolysis of desoxyribose nucleoprotein. The healing of infected wounds is enhanced by the removal of fibrin and desoxyribose nucleoprotein.

The best results are obtained where provision for drainage is adequate. The circulation to the involved area must be good. Necrotic tissue must be removed manually, since it prevents satisfactory contact of the enzymes with the wound.

Toxic effects from application to external wounds have not been seen as yet. Minor headaches, aching, and an elevation in temperature have been seen more frequently in the instances in which closed spaces have been treated. Prothrombin times have not shown significant alteration from the normal. Hematomas and areas of ecchymosis have not been seen. Bleeding has not been produced by the topical application of these compounds.

The contents of an ampule of Streptokinase, 100,000 units, and Streptodornase, 60,000 units, are readily solubie in 20 cc. of sterile isotonic sodium chloride solution. Vigorous shaking should be avoided. When prepared, the solution should be used immediately. Where divided doses of an ampule are administered, the remainder is placed in a sterile container and stored in a refrigerator.

When used as an ointment, 100,000 units of Streptokinase and 60,000 units of Streptodornase are incorporated in 10 cc. of Lubafax, a water-soluble base. The addition of antibiotics, such as aureomycin, to this suspension may prove useful to control surface infection.

To date, 19 patients with tuberculous infections, of which 14 were severe, have been treated by the methods described. These include 4 patients with tuberculous empyema, 5 patients with tuberculous lymphadenitis, and 10 patients with some manifestation of tuberculosis of the bones, joints or tendons. In 16 of these, the tuberculous infection has been controlled, and all wounds and sinuses are healed. The remaining 3 individuals had far advanced and progressive tuberculosis. Local improvement was obtained in each of these but the systemic progress of the disease continued with fatal result.

Care must be taken when Streptokinase and Streptodornase are used in the treatment of tuberculous empyema in the presence of a bronchopleural fistula, since spread of the infection may occur. This complication has not been seen in two instances so treated.

The rapidity of healing afforded by surgical drainage of tuberculous abscesses when combined with the use of Streptokinase and Streptodornase offers a more satisfactory way of treating these lesions than older conservative methods. The enzymes must be used purely as an adjunct, however, to other therapy. The compounds do not affect living tissue and facilitate the formation of healthy granulation tissue. If spontaneous closure of wounds does not occur rapidly, secondary closure may then be carried out. 14 references.—*Author's abstract.*

179. *The Treatment of Some Bacterial Infections of the Heart and Pericardium.* THOMAS H. HUNTER, St. Louis, Mo. Bull. New York Acad. Med. 28:213-28, April 1952.

The author reports on experimental observations of the effects of various antibiotics singly and in combination on large populations of nonhemolytic *streptococci in vitro.* Studies also are described of the effects of antibiotics on populations of the same organisms incorporated in human blood clots. Quantitative bacteriologic studies extending over periods up to 24 days are included. It is demonstrated that all penicillin-sensitive strains of *Streptococcus viridans* are not completely killed by concentrations of penicillin as much as 100 times the minimal inhibiting concentration maintained for as long as one week. It is further shown that high concentrations of penicillin of the order of 10 u/ml. may be required to eradicate some green *streptococci* from blood clots. Although streptomycin by itself is largely inactive against many strains of nonhemolytic *streptococci*, combined with penicillin it enhances the bactericidal activity of the latter very strikingly and the combination of penicillin with streptomycin appears to be the most active one discovered against both the *enterococci* and *Streptococcus viridans* strains studied. Aureomycin and terramycin are usually found to be largely bacteriostatic in their action, although, when combined with streptomycin, their effect is often bactericidal in liquid media. The combination of aureomycin or terramycin with streptomycin was not found to be effective in eliminating viable bacteria from blood clots. Clinical correlations with these observations are discussed. 13 references. 14 figures.—*Author's abstract.*

ONCOLOGY

180. *Further Observations on the Use of Triethylene Melamine in Neoplastic Diseases.* JUNE C. WRIGHT, AARON PRIGOT, LOUIS T. WRIGHT, AND ISIDORE ARONS, New York, N. Y. Arch. Int. Med. *89*:387–404, March 1952.

In a previous paper, the use of triethylene melamine in the treatment of 14 cases of neoplastic diseases of various types was reported. In this paper 28 additional cases are reported, with follow-up reports on 6 of the cases reported previously. Improvement was obtained in 18 of the series of 42 patients, including 9 in the group previously reported and 9 in the new group. Definite improvement was noted in 4 of 6 cases of Hodgkin's disease, 3 cases of lymphosarcoma, 2 of 3 cases of reticulum-cell sarcoma, 3 cases of chronic lymphatic leukemia, 1 cases of fibrosarcoma, and 1 case, each, of chronic myelogenous leukemia and mycosis fungoides. Two cases of Hodgkin's disease showed no favorable response; while cases of lymphosarcoma and reticulum-cell sarcoma showed a favorable response, there were no beneficial results in other types of sarcoma or in 12 cases of carcinoma. Twenty-nine of the 42 patients have died, including 8 in the group reported previously and 21 in the new group. In 2 cases, 1 of Hodgkin's disease and 1 of lymphosarcoma, in which a definite leukopenia developed following triethylene melamine therapy, the citrovorum factor was given to restore the white cell count to normal. 3 references. 10 figures. 4 tables.

181. *Mesenchymal Tumors of the Stomach.* GLADDEN V. ELLIOTT AND HUGH M. WILSON, St. Louis, Mo. Arch. Int. Med. *89*:358–67, March 1952.

In a total of 5,183 examinations of the stomach in the last 18 months, gastric lymphosarcomas were found to account for 14.3 per cent of all the gastric neoplasms found, an unusually high percentage as compared with the incidence of gastric sarcomas reported by others. In the same period 5 leiomyomas of the stomach were found—an additional 4.2 per cent of all gastric neoplasms; there was 1 other case of subserosal lipoma. In 1 of these 6 cases, there was massive hematemesis, in another repeated gastro-intestinal hemorrhages had occurred, and 2 had melena. In 2 cases the patients were admitted with a diagnosis of anemia and evidence of gastro-intestinal bleeding as the cause of the anemia was found on examination. There was a palpable abdominal mass in only 1 case; in 2 other cases the roentgenologic examination showed large masses. The most characteristic roentgenologic findings in these cases were: a sharply circumscribed intraluminal filling defect, sometimes associated with a mass projecting beyond the outline of the stomach; the obliteration of gastric rugae over the tumor with normal rugae in the surrounding region; pliable gastric walls and active peristalsis, and an evidence of ulceration in the center of the tumor in some cases. While a definite diagnosis of leiomyoma or lipoma cannot be made by clinical and roentgenologic examination, the symptoms and roentgenologic findings in leiomyosarcoma are more varied and confusing. In cases of primary lymphosarcoma of the stomach the clinical symptoms resembled those of gastric carcinoma. There were in addition, 7 cases of

lymphosarcoma of the stomach associated with generalized lymphosarcoma, in 3 of which the primary lesion may have been in the stomach. The only method of making an exact diagnosis is by means of histologic study. In the 6 cases of leiomyoma and lipoma, the tumor was diagnosed as histologically benign, but in 1 of these cases (leiomyoma with ulceration), the postoperative clinical course (with loss of weight and hepatomegaly) indicates malignancy (possibly leiomyosarcoma). 9 references. 7 figures. 3 tables.

CARDIOVASCULAR DISEASES

182. *Orthostatic Hypotension Following Chordotomy for Intractable Pain.* DONALD A. JOHNSON, GRACE M. ROTH, AND WINCHELL MCK. CRAIG, Rochester, Minn. Proc. Staff Meet., Mayo Clin. *27*:131–35, Mar. 26, 1952.

Orthostatic hypotension is fundamentally a disorder of the nervous system. The variety of neurologic lesions which may be associated with orthostatic hypotension indicates that interruption of a vasopressor pathway at various levels within the nervous system may account for the syndrome. Because anhydrosis is often associated with it, idiopathic orthostatic hypotension usually has been attributed to a hypothalamic lesion. A case is reported in which severe orthostatic hypotension followed a bilateral high thoracic anterolateral chordotomy for intractable pain. Anhydrosis was postoperatively below the level of the chordotomy. A gradual recovery of vascular and sweating functions occurred.

The similarity of this complication of chordotomy to idiopathic orthostatic hypotension suggests that some cases of the latter are due to lesions in the anterolateral quadrant of the spinal cord. 24 references. 1 figure.—*Author's abstract.*

183. *Factors in the Onset of Coronary Occlusion and Coronary Insufficiency. Effort, Occupation, Trauma, and Emotion.* ARTHUR M. MASTER AND HARRY L. JAFFE, New York, N. Y. J. A. M. A. *148*:794–98, Mar. 8, 1952.

Because of the frequency of coronary disease and the increasing number of people in industry over the age of 45, the relation of acute coronary episodes to effort, trauma, occupation, and emotion is of great scientific and medico-legal importance. In the past, there has been some disagreement concerning the relationship of effort, emotion, and trauma to coronary occlusion. We think that much of this difference is the result of not differentiating acute coronary occlusion from coronary insufficiency. The two can be separated electrocardiographically in over 90 per cent of cases.

In over 2,080 attacks of coronary occlusion only 2 per cent were found to be associated with unusual effort and reasons are given for considering the relationship coincidental. Occupation, season, and time of day did not influence the incidence of coronary occlusion. In 100 attacks of coronary insufficiency 56 began spontaneously and 44 were precipitated by hemorrhage, pulmonary embolism, effort, tachycardia, operation, excitement and meals. Angina pectoris almost always is

related to effort; coronary insufficiency is related to effort in about half the cases and coronary occlusion only rarely and coincidentally. Trauma may produce contusion of the heart or coronary insufficiency. The criteria for establishing compensability in acute coronary episodes are discussed. The following theoretical problems are considered: relationship of one attack of coronary occlusion to a subsequent one; length of disability and employability following coronary occlusion; causal relationship of effort to permanent angina pectoris. In general, the outlook for the worker after coronary occlusion is much better than was formerly thought. One half to two thirds of patients return to gainful employment within one year. In coronary insufficiency the prognosis is even better. 2 figures. 6 tables.—*Author's abstract.*

184. *Tuberculous Pericarditis. Its Treatment with Streptomycin and Some Observations on the Natural History of the Disease.* THEODORE M. MYERS AND MORTON HAMBURGER, Cincinnati, Ohio. Am. J. Med. *12*:302–10, March 1952.

Three patients with clinically primary tuberculous pericarditis with effusion, who had no clinical evidence of tuberculosis elsewhere in the body, were treated with intramuscular streptomycin for 90, 90, and 112 days, respectively. Their response was dramatic and prompted the report. When compared with 9 patients who had the same disease during the pre-streptomycin era and who received no specific treatment, it was evident that those who received streptomycin did considerably better. Although 4 of the 9 untreated patients showed spontaneous healing of the pericarditis, they were febrile for a longer period than the treated patients, and within 24 months all 4 had evidence of recurrence elsewhere in the body. The 3 patients who received streptomycin, on the other hand, are perfectly well and at the time the manuscript was submitted had been followed from 24–31 months. From observing the natural history of clinically primary tuberculous pericarditis with effusion, it became apparent that this entity and miliary tuberculosis with pericardial involvement are often indistinguishable when the patient is first seen. It also became apparent that tuberculous pericarditis may heal spontaneously and that death is usually due to dissemination rather than pericardial involvement *per se*. It also seemed that streptomycin shortened the course of the disease and improved the long-term prognosis. 13 references. 4 tables.—*Author's abstract.*

185. *Angina Pectoris in the Absence of Coronary Disease.* JAMES LEE WILSON AND SAMUEL A. LEVINE, Boston, Mass. Ann. Int. Med. *38*:897–991, March 1952.

Typical attacks of angina pectoris had occurred in 2 patients, in whom autopsy showed that the coronary arteries were normal. One of these patients was a woman 30 years of age with severe anemia, and the other patient was a man 61 years of age with diffuse amyloid disease which involved the myocardium. In a review of the literature it was found that other rare cases of anemia with attacks of angina and without coronary artery disease have been reported. Also a small "but not insignificant" number of cases have been reported in which anginal attacks occurred in

cases of heart disease without involvement of the coronary arteries—valvular disease (aortic or mitral) and hypertensive heart disease, but no other case of angina in amyloid disease of the heart was found. 10 references. 2 figures.

RESPIRATORY DISEASES

186. *Diffuse Interstitial Fibrosis of the Lungs.* ELI B. RUBIN, BERNARD S. KAHN, AND DAVID PECKER, New York, N. Y. Ann. Int. Med. *38*:827–44, March 1952.

In the case reported the patient was a 44 year old woman; when first seen at the hospital she had a cough with thick mucous sputum and dyspnea on exertion; the only physical sign elicited was the presence of rales in the left lower lobe; the x-ray examination showed exaggeration of the pulmonary markings in both lungs. Dyspnea and cough became more severe; she was twice readmitted to the hospital, and treated in an oxygen tent; she died suddenly with symptoms of acute respiratory failure 4 days after being discharged from the hospital, 2 years and 4 months after her admission. The diagnosis of interstitial pulmonary fibrosis, as described by Hamman and Rich in 1944, was based on the manner of death, rather than on the course of the disease. It was confirmed at autopsy. A review of the literature showed 13 other cases of diffuse interstitial fibrosis of the lungs, including the 4 reported by Hamman and Rich, which are briefly summarized. The chief symptoms in all cases were cough, with varying amounts of sputum, chest pain, occasional hemoptysis, fever, and increasing dyspnea and cyanosis; clubbing of the fingers and toes occurred in some cases, including the authors' case. In most cases the onset of the disease was sudden, but in some cases gradual and insidious; the duration of life after the onset of symptoms varied from 34 days to $3\frac{1}{2}$ years. Autopsy in these cases showed diffuse interstitial fibrosis involving both lungs and thickening of the alveolar septa, which were partially replaced with hyalinized connective tissue; different stages of the fibrosis were found in various areas of the lungs. In most cases there was cardiac enlargement, chiefly of the right heart. The authors are of the opinion that this disease is caused by a virus, the fibrosis in the lung representing one form of tissue reaction to this virus, which may be associated with involvement of other tissues. It is possible that recovery may occur in some cases, but this cannot be proved as exact diagnosis must depend on the autopsy findings. 11 references. 7 figures.

BOOK REVIEWS

Antibiotic Therapy. HENRY WELCH, PH.D. AND CHARLES N. LEWIS, M.D. (With a Foreword by Chester S. Keefer, M.D.) The Arundel Press, Inc., Washington, D. C., 1951.

The recent advances in the chemotherapy of infectious diseases and the introduction of the newer antibiotic agents have revolutionized therapy. However, although more may be done for the patient, the physician has been presented

with a complex problem in the selection and use of each of the antibiotic agents, its indications, and contraindications.

Dr. Welch and Dr. Lewis have performed a distinct service in assembling the data on the various antibiotics. A short history of each, with a description of its isolation and pharmacology, is presented. A very happy addition is the biographical sketch of the individuals who have contributed to the isolation of these newer antibiotics.

In addition to the *in vitro* antimicrobial spectrum, there are chapters on the common bacterial, spirochetal, viral, and rickettsial diseases. These are well organized in that a short review of the clinical course is appended before the detailed specific antibiotic therapy is discussed. Not only are the recommended antibiotics and their dosage outlined, but intimate details as to dosage-schedule and the various forms in which the antibiotics are available for clinical use are included.

The completeness of this book is impressive and it is vastly superior to many of the so-called comprehensive compilations that have been previously offered to physicians. An extensive bibliography is appended to each chapter and the index will be found most helpful. —*Emanuel B. Schoenbach, M.D.*

Tumors of the Carotid Body and Related Structures (Chemoreceptor System). PHILIP M. LE COMPTE, M.D., Boston, Mass. Atlas of Tumor Pathology, Section IV, Fascicle 16, Published by the Armed Forces Institute of Pathology, Washington, D. C., 1951. 40 pages, 23 figures. Price: 45 cents.

This is another in the series of monographs on tumor pathology published by the Armed Forces Institute of Pathology and the National Research Council. The increasing recognition of tumors of the carotid body, and structurally similar tumors arising elsewhere, has aroused great interest. Much confusion surrounds the classification of these tumors. The present monograph is well organized and illustrates clearly the various aspects of the problem. It is wholeheartedly recommended. —*Emanuel B. Schoenbach, M.D.*

Blood Clotting and Allied Problems. Transactions of the Fourth Conference, January 22 23, 1951. Edited by JOSEPH E. FLYNN, Department of Pathology, College of Physicians and Surgeons, Columbia University, New York. Josiah Macy Jr. Foundation, New York, 1951. 272 pages, 27 tables, 81 figures. Price: $4.00.

This conference on the problems of blood clotting has, as usual, a distinguished group of participants under the chairmanship of Dr. Irving S. Wright. In the words of the medical director the answer to many problems attracting the interest of investigators in the medical sciences will not be served by "further fragmentation into increasingly isolated specialties, disciplines and departments but by integration of . . . scientific knowledge of all branches."

The conference deals with the problems of blood clotting in its various aspects including the physiology of the circulation so ably presented by Dr. Knisely, the complex components of clot-formation and the chemistry of the protein moieties which participate in the process. The thesis in each section is ably presented and the discussion which is interspersed or appended is critical and illuminating. Perspective as to the status of our knowledge and the basic premises of current theories is attained.

This presentation is in keeping with the other conferences published by the Josiah Macy Jr. Foundation and is recommended to students, physicians and those in allied fields as a dynamic and informative presentation.—*Emanuel B. Schoenbach, M.D.*

Adrenal Cortex—Transactions of the Second Conference, November 16–17, 1950. Edited by ELAINE P. RALLI. Josiah Macy Jr., Foundation, Progress Associates, Inc., Caldwell, N. J. Price: $3.00.

This is another valuable and timely discussion on the problems of adrenosteroids and adrenocortical function. The general topics covered are: the present status of ACTH; regulation of pituitary adrenocorticotropic activity; the relation of the adrenal cortical hormones to the hypersensitive state; hyaluronidase and the adrenal cortical hormones; further clinical studies with ACTH and adrenal cortical hormones.

This type of presentation is most stimulating in that it is not a formal, but a free and active discussion. These conferences are not designed for the general practitioner, but they are highly recommended for students and individuals interested in this particular field. Much more is offered in this symposium than is indicated by the factual data. The attitude and criticisms provide very valuable additional knowledge. The clinical studies indicate the direction in which future developments of our knowledge of adrenocortical function may be applied.

This conference, as the others in this series, makes one feel that one is participating in the discussion.—*Emanuel B. Schoenbach, M.D.*

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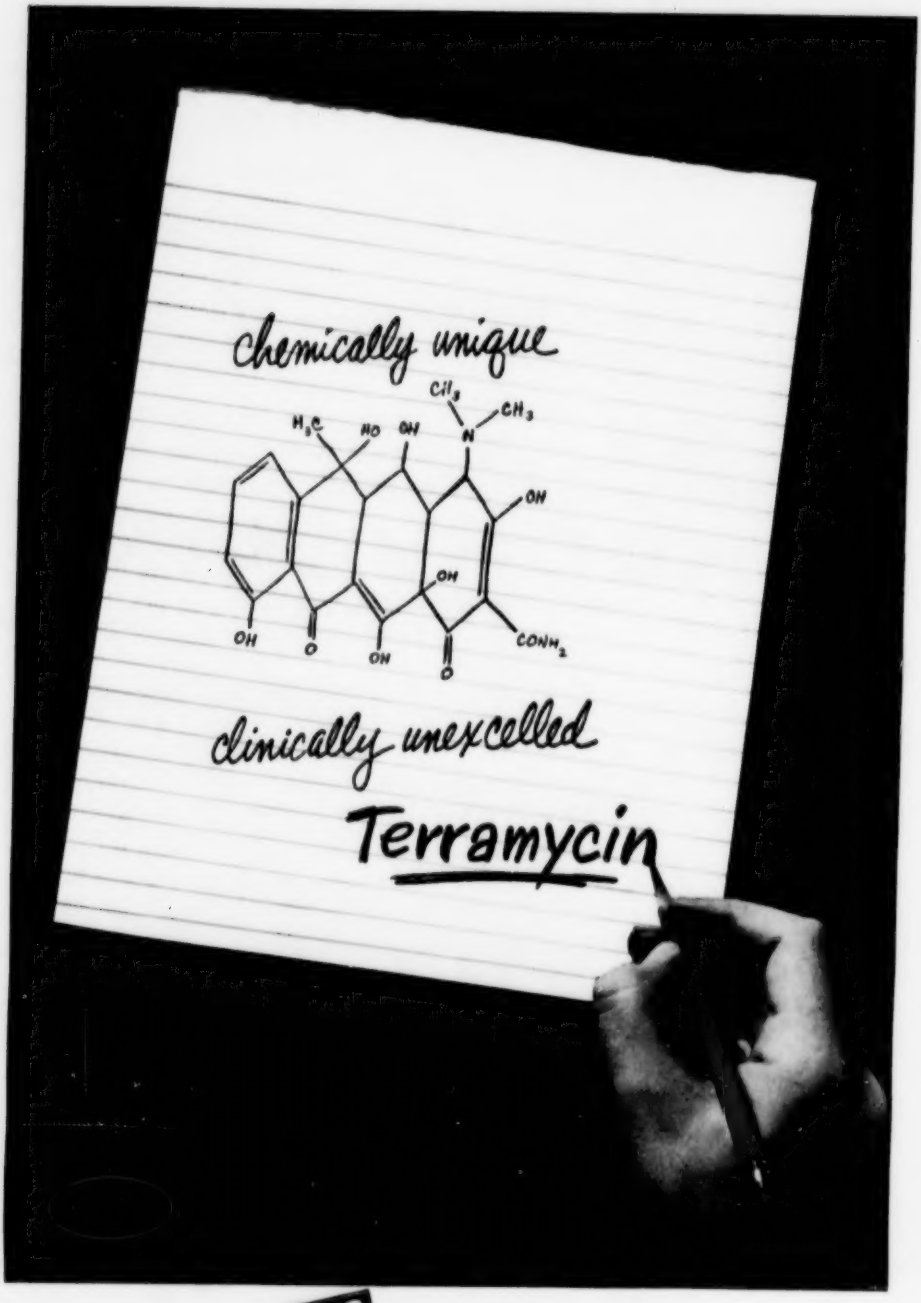

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